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NATIONAL INSTITUTE OF MENTAL HEALTH

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U.S. NATIONAL INSTITUTE OF MENTAL HEALTH

Annual Report for the Calendar Year 1960

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BIOMETRICS BRANCH

ANNUAL REPORT FOR CALENDAR YEAR 1960

General

The Biometrics Branch has made continuing progress in each phase of its program which consists of the following activities:--(a) collecting, processing, and analyzing data on the extent of the problem of mental disorders particularly with regard to patients under treatment in mental hospitals and outpatient psychiatric clinics, in general hospitals with psychiatric services, and in public and private institutions for the mentally retarded; (b) providing consultative services to state research bureaus on the organization of statistical services and on the design of followup, evaluative and other special studies; (c) providing consultative services on design of experiments, analysis of experimental data and development of mathematical models to the other Branches and Laboratories of the Institute, particularly to personnel engaged in basic and clinical research.

A primary function of the Biometrics Branch is to provide basic data and develop methodology for evaluating state and local programs designed to prevent mental disorders and to reduce disability associated with these disorders. Because of the broad scope of the problem and the complexities of evaluation in this field the Biometrics Branch has concentrated its efforts, for the time being, on developing for each state a systematic body of reasonably uniform statistical data of persons under treatment in mental hospitals and outpatient clinics. This kind of action was decided upon for two major reasons--first, it appeared impossible to obtain data on the incidence and prevalence of mental disorders in the general population of the various states; second, since many state departments of mental hygiene have already developed statistical reporting systems for gathering data on the characteristics of a large number of patients for whom they provided care, it seemed reasonable to make use of these organized data collection activities as a wedge for developing a systematic body of statistical and epidemiologic data concerning the mental disorders in each state.

The Branch has made considerable progress in the collection of data on patients under treatment in mental hospitals and outpatient psychiatric clinics. Nevertheless, the task of collecting data on the fate of patients remains an extremely difficult task because of the lack of certain essential knowledge on the etiology and epidemiology of the mental disorders and the absence of instruments that can be used in comparable fashion from institution to institution or from clinic to clinic to determine severity of illness and to characterize the psychologic status, the degree of psychiatric disability, social and familial adjustment, and physical condition of patients at various intervals following onset of disease. As more new therapeutic programs and types of treatment facilities are introduced the task of obtaining data on people under treatment becomes increasingly difficult and complex, and data derived from separate treatment facilities such as public mental hospitals, outpatient clinics and psychiatric facilities of general hospitals become increasingly

difficult to interpret. It has become quite apparent that state mental health and state mental hospital authorities must develop statistical reporting programs that will coordinate basic data on patients under treatment in all known psychiatric treatment facilities in their jurisdictions which will include appropriate followup data on the various classes of patients. One of the major problems in this regard is the fact that as a result of differences in community organization, of relationships between official and voluntary agencies, of availability of personnel and of characteristics of the population groups being served, considerable variation also exists in the way agencies responsible for various elements of these programs implement and coordinate their activities at the state, county, city and local levels.

With the increasing interest in specific areas impinging upon mental illness and mental health there is a need for programs which would coordinate data on all of the social, emotional and behavioral problems in a community. Thus, to accomplish this purpose and to provide administrators of mental hospital and outpatient clinic programs a perspective within which they can evaluate their own programs reporting is needed in defined geographic areas from such sources as private psychiatrists, social agencies, juvenile courts, facilities for alcoholics, nursing homes, chronic disease hospitals and homes for the aged. Preliminary discussions regarding such reporting have been held with members of the Community Services Branch.

The Branch has been working with the states to improve reporting within public mental hospitals and outpatient psychiatric clinics. The Model Reporting Area for Mental Hospital Statistics now includes 22 member states. The hospitals in these states account for 208 of the 281 state and county mental hospitals of the nation and provide care for approximately 75 percent of the patients in all state and county mental hospitals on any one day. The statistical systems of two additional states have been inspected for possible membership in the Area and one further state has applied for membership. The addition of these three states would bring the representation of the Model Reporting Area to approximately 80 percent of the nation's mental hospital population. The activities of the Model Reporting Area have stimulated the further development of regional groups of mental health statisticians with a continuation of annual meetings of a Midwest group and a Southern group. Participation by psychiatric clinics in national reporting has continued to improve. Approximately 1060 of the 1430 clinics now report information on patient services. Regional meetings were held with representatives of all of the state mental health authorities and personnel from individual clinics to review the national reporting program and to consider the modifications in definitions and items of information collected. As a result of these meetings major revisions are being made in the format in which data are being reported annually by the states so as to provide greater flexibility and variety in the resulting tabulations.

The services of the Section on Theoretical Statistics and Mathematics continued to be in increasing demand by the investigators in the basic laboratory and clinical research programs of the National Institute of Mental Health. This section has been engaged in building deterministic and probabilistic models in areas such as polymer chemistry, active transport, the blood-brain barrier, psychology, and kinetics. Advice has also been provided to different

committees with regard to grants, surveys, and proposals in the field of mental health.

The achievement of results in the biometrics field has been slow. One factor contributing to this is the shortage of well qualified personnel to fill positions both in the NIMH and in the state and local programs. Furthermore, in many instances the directors of state and local mental health programs are not sufficiently impressed with the importance of the role which good statistical analysis can play in their programs. In general, much must be done to improve the communication between the administrators of mental health programs and the statistician. All too often the statistician in charge of statistics and research for a mental health department does not have sufficient guide lines from his administrator to indicate the administrator's needs for data. Thus, it is necessary for the statistician to anticipate the needs of the administrator and to develop statistical reporting and analyses which he believes will be useful. Unfortunately, however, many of the personnel working in these statistical positions are not sufficiently well trained and are, therefore, not capable of developing statistical programs without very thorough guidance from the administration of their departments. Thus, this situation can be improved only by motivating the administrator to make his needs known clearly and to provide guidance to those individuals operating statistical programs so that answers to important questions can be obtained.

Because of the close interrelationships among the problems handled by the Hospital Studies, the Outpatient Studies, and the Consultation Sections, several problems have been approached cooperatively among these Sections. The specific activities involved in these cooperative efforts are described in the report of the section primarily responsible for them. The reports of the individual sections follow:

HOSPITAL STUDIES SECTION

During the year the Hospital Studies Section continued its work in further developing the Model Reporting Area for Mental Hospital Statistics, carrying out cooperative studies with individual hospitals and state mental hospital systems on methodology of cohort studies and on the development of studies designed to assess the role of the hospital in the care of patients, and work with the Outpatient Studies Section in initiating a study which will relate the socioeconomic characteristics of persons admitted to psychiatric facilities to corresponding characteristics of the general population.

Tenth Annual Conference of Mental Hospital Statisticians. The Model Reporting Area for Mental Hospital Statistics held its tenth annual meeting in Bethesda, Maryland in May 1960. The acceptance of Tennessee into the Area brought the total number of member states to 22, representing approximately 75 percent of the public mental hospital population in the country. The Conference discussed the possibility of conducting studies to determine the effect of drug usage on the movement of mental hospital populations. Such studies would provide a prototype for similar analyses of other new therapies as soon as possible after they are introduced. It was agreed that the Biometrics Branch would investigate the several problems which were raised and would then develop a protocol for the study. A discussion was devoted to the problem of the interaction between the mental hospital and the large variety of facilities in the community organized to care for the mentally ill. It was agreed that considerable future effort of the Model Reporting Area should be devoted to developing methods of evaluating the effect of these programs. A committee met in March 1960 to discuss the problem of collecting adequate data on mental hospital personnel on a national scale. In a report of this committee meeting, which was presented at the Conference, it was proposed that a more meaningful classification of mental hospital personnel be developed in which such personnel would be classified according to the functions they perform. It was agreed that the Biometrics Branch, in cooperation with experts in the field, would develop definitions for the proposed categories of personnel.

Cohort Studies. A report of the first cooperative study conducted by the Model Reporting Area was published in November 1959. In this study groups of first admissions with specified characteristics were followed during the first twelve months of hospitalization to determine their probabilities of release, retention and death. A large section of the monograph was devoted to a discussion of pitfalls and difficulties inherent in these and other hospital data among the 11 states.

Most of the states in the Model Reporting Area are cooperating in another cohort study which will attempt to eliminate many of the pitfalls of the first one by more precisely defining categories of patients and by using a longer followup period. The study will obtain probabilities of first release and death and, in addition, provide the probability of return to the hospital within specified periods following first release among cohorts of released patients. Collection of data for the study began on July 1, 1959 and will continue for a three year period.

The Biometrics Branch has continued to work with the Warren State Hospital, Warren, Pennsylvania. Data have been obtained that make possible analyses of the experience of cohorts of first admissions to this hospital during the period 1926-58, not only by age, sex and diagnosis but also by such variables as urban-rural residence, occupation, marital status, therapies, etc., and provide a basis for determination of readmission rates to the hospital by specified periods of time following release and all the previously mentioned variables. Problems in coding have been worked out and the data are now being processed for tabulation. Data on admissions during the years 1948-52 were used as a basis for developing efficient data processing procedures using a relatively small number of cases. Also, since these years are centered around the 1950 census of population, patients' admission characteristics can be related to the characteristics of the general population. For example, preliminary findings reveal some striking geographical variations in admission rates with respect to both distance and direction from the hospital. A comparison of probabilities of release in relation to the use of tranquilizing drugs revealed that those who had received drugs had a considerably lower probability of release as compared with those who had not received drugs. Criteria for selection of patients for drug therapy and the hospitals' philosophy of drug usage are now being studied. More detailed analyses of admission patterns, therapy, and movement of patients will be carried out jointly with hospital personnel.

Socioeconomic Study. The study of the demographic, socioeconomic and family characteristics of patients admitted to psychiatric facilities in 1960 has been initiated in Maryland and Louisiana and, on a more limited basis, in Indiana and Pennsylvania. This study, being conducted in conjunction with the Outpatient Clinic Section, has as its primary objective the determination of the extent to which various socioeconomic groups utilize the different psychiatric facilities within a state. In order to attain this objective, it is necessary to have basic socioeconomic data on the patient and members of his family which can be related to similar data obtained for the general population in the 1960 U.S. Census.

In Maryland and Louisiana basic identifying information is being obtained for each patient admitted to the public and private mental hospitals, the outpatient psychiatric clinics, psychiatric services of general hospitals, and the inpatient and outpatient psychiatric facilities of the Veterans Administration during the period July 1, 1960 to June 30, 1961. This information will be given to the Bureau of the Census which will attempt to locate the corresponding 1960 census schedules for these individuals. The Census Bureau will then tabulate detailed socioeconomic and family characteristics of these individuals and will prepare similar tabulations of the populations of these two states.

A pilot study was carried out in North Carolina, where a pilot census had been conducted, to determine what problems would result in attempting to match names of admissions to psychiatric facilities against census schedules. A major finding of this pilot study was the fact that matching was more difficult in rural areas than in more highly urbanized areas. Thus, steps are now being taken to improve address reporting by patients. In order to estimate the characteristics of the group of patients and their families for whom the

Census Bureau will not be able to locate census schedules, a detailed study is being made of a 10 percent random sample of the admissions to the psychiatric facilities described above. Each of the individuals included in the sample is providing the interviewer with detailed information identical to that obtained by the Bureau of the Census during its 1960 population census.

In Indiana and Pennsylvania, detailed socioeconomic and family data, identical to those obtained by the Census Bureau, are being obtained for each admission to all of the state mental hospitals for a one-year period. Comparisons of these data with the state mental hospital data from the Maryland and Louisiana studies will provide a basis for making inferences about admissions to other psychiatric facilities in Indiana and Pennsylvania.

Mental Hospital Personnel. In March 1960 the Biometrics Branch convened a committee consisting of mental hospital administrators, personnel officers, and statisticians to discuss a revision in the national reporting of mental hospital personnel data. It was agreed that a revision was necessary because (1) the present classification of personnel is inadequate and ill-defined and (2) the ratios of specific categories of personnel to the total resident population of a hospital or a state mental hospital system are inadequate to describe the staffing of mental hospitals. The major accomplishment of the committee meeting was the development of a first draft of a revised personnel classification in which each category of personnel was subdivided according to professional and special training qualifications. It was proposed that the Biometrics Branch develop comprehensive definitions for each category in consultation with experts in the field and that these then be distributed among the states for comments and suggestions.

Considerable interest was expressed in the routine reporting of personnel turnover data. It was suggested that for each category of personnel the following items be reported: Number employed at beginning of year, number added during the year, number leaving employment during the year, and number employed at end of year. A personnel turnover ratio could then be computed by dividing the number of personnel leaving employment during the year by the average number employed during the year. The committee also enumerated a number of areas of special interest related to mental hospital personnel which would be suitable for special study. Among these were trends in the use of patient labor for farm operations, bakeries, etc., a study which would define the significant segments of the hospital population to which numbers of personnel in specific categories should be related to measure the deployment of hospital staff, a survey of the availability and use of training programs and their relationship to personnel turnover, and a study of accident rates among personnel and among patients.

Regional Meetings. The Sixth Midwest Conference on Mental Health Statistics was held in Columbus, Ohio in October 1960. These meetings are an outgrowth of the annual meetings of the Model Reporting Area and are quite helpful to representatives of midwestern states who are not members of the Model Reporting Area. A working committee met in January 1960 and formulated the details for a cooperative interstate study on aged mental patients, which was the primary focus of the 1959 Midwest Conference. The study, a special cohort analysis which is patterned after that being carried out by the Model

Reporting Area, was approved by the Conference and six of the ten midwestern states planned to participate.

The balance of the Conference was devoted to a variety of topics including reporting problems for the public mental hospitals, public institutions for the mentally retarded and the outpatient psychiatric clinics. The form and content of future Midwest Conferences was considered and plans were made to include a one-day workshop on administrative uses of statistics. As was true for past meetings, representatives of the Biometrics Branch played a major advisory role at this Conference.

A similar group was organized among the 16 states in the region served by the Southern Regional Education Board late in 1959. One of the primary objectives of this group is to attain comparability in mental health statistical data and uniformity in reporting these data based on standard definitions already developed by the Model Reporting Area. Eight of the states in this region are now members of the Model Reporting Area and it is the goal of the group that the remaining 8 states become members. The first meeting of this group was held in January 1960 and the second annual meeting in November 1960. Among their achievements are a series of exchange visits among mental health statisticians to acquaint those beginning statistical reporting systems with procedures already in operation in other states; investigation into the possibility of holding a training institute in basic statistics oriented towards mental health problems for those with little or no training in the field; and preliminary discussion and appointment of a committee to further investigate the possibility of conducting cooperative interstate research projects. The Chief of the Hospital Studies Section has worked very closely with the Southern group during the developmental phase.

The Section assisted the Consultation Section in providing advice and recommendations in the development or revision of statistical reporting systems to programs in West Virginia, Idaho, Virginia, Indiana and Connecticut. The Section Chief and one of the statisticians participated in the inspection of statistical systems in Oregon and Idaho respectively for purposes of satisfying requirements for membership in the Model Reporting Area. The staff of the Section also consulted with personnel in state programs on a variety of problems such as development of data for drug studies, a multivariate analysis on factors associated with successful stay in the community following release from the hospital and processing of data for a followup analysis of mental hospital admissions.

CONSULTATION SECTION

The Consultation Section has continued to furnish advice and assistance in research design, data collection and analysis in order to procure much needed administrative, clinical and epidemiological information. Toward these objectives, continuing efforts have been made to establish efficient record systems and to increase the use of comparable terminology and definitions. These efforts have been hampered, in part, by a shortage of well-trained people and by salary levels which are noncompetitive in attracting qualified people to the field in general and to these agencies and facilities in particular.

The following states or agencies requested and received consultative services regarding improvement of their central office, mental hospital or outpatient psychiatric clinic record systems or on matters regarding research design, program evaluation and data analyses: Alabama, California, Connecticut, Florida, Hawaii, Indiana, Kansas, Maryland, Massachusetts, North Carolina, North Dakota, Ohio, Oregon, Virginia, West Virginia.

Alabama. Field trips were made to Bryce Hospital, Tuscaloosa, at the request of the Superintendent. The medical record system was reviewed for its adequacy in providing information for reporting purposes in connection with Model Reporting Area membership, and in serving patient care needs and meeting minimum standards for hospital accreditation. Recommendations were made and help given in planning a more adequate medical record program, in implementation of basic procedural changes, in defining medical record functions and reorganizing the medical record department, and in establishing a medical record committee.

Further assistance should be given in improving content and use of record data and in developing the statistical reporting program.

California. Consultation on medical record aspects of medical data automation research projects was provided to Pacific State and Camarillo State Hospitals at the request of the Superintendent and Research Director, respectively. Suggestions were made for integration of special project records or special record systems into the established hospital record system at the completion of such projects.

Assistance in recruitment of a Medical Record Librarian was given to the Medical Director of the Los Angeles Probation Department at his request.

Consultation was afforded the Director of the Los Angeles Suicide Prevention Center on techniques in abstracting data from records of long-term hospital patients.

Connecticut. Conferences were held with the Commissioner of Mental Health and members of his staff on recordkeeping problems of mental hospitals of the state system. Plans were reviewed and recommendations made for remodeling the medical record department at the Norwich State Hospital. A followup on our recommendation for changes in the record system at Connecticut State

Hospital, Middletown, was requested by the Clinical Director of that hospital and our findings were reported to him and to the Commissioner.

Florida. Consultation was provided to a coordinated community program which had been set up with a Mental Health Project Grant to assist patients returning from mental hospitals. Records and reporting procedures were reviewed and revised to assure their adequacy to determine the number and characteristics of patients being served, the services recommended and received, and some measures of results.

Hawaii. Assistance will be provided in the development of a central records system for the control of patient flow into, through, and out of all the units of the Division of Mental Health of the Department of Health.

Indiana. The current and proposed National Institute of Mental Health clinic reporting program was reviewed: definitions, report forms, tabulating procedures, annual and other interpretive reports. Suggestions for special studies and administrative research were presented.

Kansas. Conferred with superintendents of schools for the mentally retarded regarding the use of the revised manual on terminology and classification in mental retardation.

Maryland. Brief visits were made to the Maximum Security Hospital at Jessup to review medical record forms, policies and procedures with the superintendent. A number of the suggested revisions in forms and procedures were accepted.

In conjunction with the Psychopharmacology Service Center of the National Institute of Mental Health, reviewed the mechanisms for recording drug usage and the feasibility of conducting such studies at the hospital with its Director of Research.

Massachusetts. The medical record system at Worcester State Hospital was reviewed. The record problems and inadequacies observed were discussed with the Clinical Director and recommendations made for development of a medical record program which would answer more effectively research and training needs of the hospital as well as those of patient care and administration.

North Carolina. Consultation and assistance was afforded to nurses and records and procedures analysts regarding a register of services and activities provided by local health departments participating in an after-care program for the mentally ill.

North Dakota. At the request of the Superintendent of the State Hospital at Jamestown, the hospital's medical record program was reviewed and the status of qualification for Model Reporting Area membership was investigated. Recommendations were made for changes in the medical record system for reassignment of some medical record functions and for continuation of preparation for Model Reporting Area participation. This visit was made in conjunction with consultants from Community Services Branch and Regional Office VI.

Ohio. Proposed projects of the Research Director, Alcoholism Unit, Ohio Department of Health, were reviewed.

Consultation was provided at the Cleveland Psychiatric Institution for the purpose of making its recordkeeping system more suitable for research. Proposed research projects were reviewed.

The Section is continuing its utilization of records from the Ohio Department of Mental Hygiene and Corrections. Data on first admissions during the years 1948-1952 have been correlated with pertinent 1950 census information. Last year a report with regard to mental diseases of the senium was presented at the American Public Health Conference and the paper was published in the Journal of the American Public Health Association. A paper reporting on alcoholic psychoses was published in the Quarterly Journal of Studies on Alcohol. A report involving immigration and insanity was published by Public Health Reports. The subsequent course of events for these admissions is now being analyzed and will be reported on during the forthcoming year. Verbal agreements have been reached assuring us of similar data for the period 1959-1961 which can be correlated with the 1960 census and permit comparisons between the two census periods of 1950 and 1960.

Oregon. Consultation on medical record problems was requested by the Director of Research at the Salem State Hospital. This was provided as was a brief review of the medical record system. The problem areas identified were discussed with the Superintendent and the Medical Record Committee and recommendations made.

Virginia. At the request of the Nursing Consultant, Virginia Department of Mental Health, attended a conference of Directors and Instructors of Nurses from Virginia State Mental Hospitals, and gave an informal talk on medical records in mental hospitals.

At the request of the Director of Nurses, Petersburg State Hospital, nursing records and record procedures were reviewed. A review of the medical record system of the Virginia State Mental Hospitals has been requested by the Commissioner.

West Virginia. Consultation on the statistical reporting system and medical record problems related to it was provided by the Section at the request of the Director of the Department of Mental Health. The Medical Record Librarian is scheduled to visit all six of the West Virginia State Mental Hospitals, review the medical record systems and recommend any changes indicated.

Other Activities. The Chief of the Section served as the statistical consultant and his assistant served as medical record librarian consultant to the Hospital Consultant Services of the Community Services Branch. As such, they participated in a survey of the Springfield Medical Center at the request of the Bureau of Prisons of the United States Department of Justice. Recommendations regarding needed revisions, new programs, personnel or facilities were made.

Conferences were held with personnel in several of the Regional Offices regarding the clinic reporting program and other mental health programs and activities with which the Biometrics Branch has an interest and in which it might make a contribution.

The Chief of the Section served as consultant and resource person in a meeting at the United States Public Health Service Hospital, Lexington, Kentucky, attended by representatives from the United States Public Health Service Hospital at Fort Worth, Texas, and personnel from the Division of Hospitals, Bureau of Medical Services. The records kept on drug addicts and their processing by the Division of Hospitals were reviewed and recommendations regarding revisions were made.

Statistical assistance continues to be provided to the Director of the United States Public Health Service Demonstration Center, New York City. Statistical analyses of the followup data regarding persons discharged from the Lexington Hospital in Kentucky is underway.

Both the Section Chief and the Medical Record Librarian participated in the Sixth Midwest Conference on Mental Health Statistics in Columbus, Ohio. The Medical Record Librarian gave an informal talk on functions of medical record librarians with special reference to mental hospitals and departments of mental health. This meeting is more fully described in the Hospital Studies Section.

The Section Chief supervised a study under contract with the Baltimore City Health Department. This study examined the concordance between elementary school teacher and psychiatrists for the purpose of determining the feasibility of using such teachers as a case finding resource in epidemiological investigations involving emotionally maladjusted school children. A detailed report of the findings is now in preparation.

The Section Chief, under the guidance of the Branch Chief, provided assistance to the Director of Reaearch and Statistics of the Health Insurance Plan of Greater New York in developing a Special Grants application in order to study patterns of medical care related to mental illness.

Served as consultant to the Mental Health Special Task Froce at the Second National Conference on Evaluation in Public Health jointly sponsored by the American Public Health Association and the School of Public Health, University of Michigan at Ann Arbor. There were seven such special task forces and eventually each report will be combined to form a manual for the use of the Local Health Officer.

The Medical Record Librarian gave a paper on "Microfilming Techniques," at the Third International Congress on Medical Records held in Edinburgh, Scotland. The paper was published in the Proceedings of the Congress. She visited mental hospitals in Edinburgh, Scotland, and in Colchester, Epsom and London, England.

OUTPATIENT STUDIES SECTION

The Outpatient Studies Section continued to work on extending the annual statistical reporting program to additional clinics, on increasing the uniformity in interpretation of items and definitions by all clinics, on the preparation of analyses for publications, and on developing revisions in the reports to more adequately reflect the characteristics and activities of the clinics and to provide more meaningful data about patients. The development of special studies to provide better understanding of the clinic population and the services they receive also has progressed during the year. The Section has completed a comprehensive study of outpatients in one State and also initiated and developed plans for coordinated research on individuals under care of all outpatient and inpatient psychiatric facilities in this state. The Section has begun to study the problems in collecting data on mentally ill persons receiving mental health services from nonpsychiatric resources.

Annual Statistical Reporting Progress. Clinic participation in the annual statistical reporting program has increased steadily since 1954-55 when the program was initiated. In that first year most of the 1,200 clinics in the United States reported information on clinic characteristics and staff and man-hours, but only 404 clinics reported data on characteristics of patients and the services they received. Special efforts to develop procedures for state tabulation of clinic data on patients has resulted in a gradual year-to year increase in the number of clinics reporting these data. In 1959, 95 percent of the 1,429 clinics in the country reported on their professional staff, 74 percent on patient information, and 58 percent on community service activities.

Continuing effort has been directed toward helping states develop complete and accurate reporting and uniform interpretation of definitions, and toward increased clinic participation in the voluntary nationwide reporting program. With the assistance of the regional mental health consultants, a series of regional meetings with representatives of all State Mental Health Authorities and individual clinics were held during the past six months, in order to review the national reporting program, and to consider modifications in definitions and items of information collected (in part based upon experiences in the Maryland Study) and in tabulation plans. As a result of these meetings, substantive revisions are being made in the format in which the data are being reported annually by the states so as to provide greater flexibility and variety in these tabulations and to facilitate the preparation of national summaries. Data will be sought on special symptoms or problems such as excessive drinking of alcohol, juvenile delinquency, and suicidal tendencies. Imrpessions of psychiatric disorder as well as diagnoses will be reported by a number of states. Committee meetings on some of the more important remaining problem areas are planned for the near future.

Extension of Reporting to Other Outpatient Mental Health Facilities. At the meetings with the states, the question of the feasibility of broadening the reporting universe to include mental health services not under a psychiatrist's direction such as psychological and marriage counseling centers,

student health services, family service agencies, child health and development clinics, and alcoholic clinics, was discussed. Such a move is considered because the demarcation between psychiatric clinics and other mental health facilities is a difficult one, because all types of mental health services have similar functions and because many mentally ill persons receive mental health services in non-psychiatric settings. Methodological exploration is underway, working with limited geographic areas, to determine (a) what new definition of a reportable mental health facility and possibly of a mental health patient may be necessary; (b) the kinds of reports these mental health facilities now prepare; (c) the kinds of data, including psychiatric description or impressions, these facilities could report; (d) the ability of the State Mental Health Authorities to assist in the data collection and tabulation processes for these facilities.

Clinic Staff. Following special publicity sent to all States on the use of 1959 data for the new clinic directory, reports on clinic characteristics and staff were submitted by 1,400 clinics in the United States. These clinic reports were made available to the National Association for Mental Health, Inc. for preparation of a 1959 Directory of Outpatient Psychiatric Clinics. This Directory should be available for distribution after the beginning of 1961.

These data have also been used for preparation of a report highlighting gains in outpatient psychiatric services since 1955, which appears in the November 1960 issue of Public Health Reports. Detailed tabulations of professional staff, by state, have been distributed to State Mental Health Authorities, and a detailed analysis including trends since 1955, is in preparation.

Patient Services of Clinics. Preliminary tabulations of the reports for 1959 on the movement of patients have been distributed to State Mental Health Authorities. A summarization of the characteristics of patients terminated during the year is being prepared. Analysis of changes in the characteristics of patients and the services they received in 1959 as compared with 1955, are planned. This analysis will include selected findings from the uniform punch cards collected nationally during fiscal year 1957.

Community Services of Clinics. The first article on the community service activities of outpatient psychiatric clinics was accepted for publication in Public Health Reports. The analysis, based on reports for April 1958 by 595, or 43 percent, of the clinics in the United States shows that these clinics devote, on the average, 6 percent of their total professional staff time to this aspect of clinic service. For the clinics that reported to date there is little evidence of any change in the proportion of clinic time spent in this activity during the past several years. Marked seasonal variation in community service activities is evident from special reports submitted by 101 clinics for each of 12 months during 1956. National reporting of this activity for every month of the year is being encouraged. In addition, the feasibility of collecting more intensive data on clinic consultation and educational processes is being investigated with interested states.

Methodological Studies in Maryland. A comprehensive research study was completed on patient characteristics and services in outpatient psychiatric clinics in Maryland, initiated during 1958 as another special project undertaken to understand needs and progress in the area of dealing with the major health problem of mental illness. This project was developed to answer searching questions on the kinds of people being seen, the services they receive, reasons for termination, and recommendations made at termination. The work in Maryland concentrated on developing and testing new classifications and definitions to develop improvements where possible; on securing total participation in the reporting program so that admission and termination rates could be obtained; on testing the extent to which a patient count for all clinics represents a duplicate count of individuals being served by clinics in an area; on an extension of life table methodology to describe the duration and type of service received by clinic patients; and on the development and application of other statistical methods in the analysis of data in the clinic area.

Nationally, diagnostic information has been lacking on 22 percent of the patients terminated from outpatient psychiatric clinics. Various methods were tested in Maryland to reduce the proportion of patients reported without a psychiatric description. As a result of these methods only 2 percent of the Maryland patients were reported with "psychiatric disorder not stated." Progress has also been made toward the solution of problems related to (1) reporting, as separate patients, mentally ill parents seen in child guidance clinics on behalf of their child; (2) defining the time period when services should be classified as terminated; (3) obtaining statistics on the symptom of problem drinking independent of the psychiatric classification. The first age specific, diagnostic termination rates in the clinic area and the first cohort analysis on the probability of being removed from the clinic rolls or receiving a final interview within specified intervals after admission were prepared.

Findings on various aspects of this study have been presented at several national professional meetings, in articles for professional journals, and in a Public Health Monograph now in press. Further cohort analyses based on a larger series of admissions and additional variables are underway; these findings are scheduled to be presented at additional scientific meetings.

Coordinated Research on Psychiatric Patients in Maryland. Special plans were initiated and developed in the Maryland project to collate information on patients in hospitals and clinics in order to develop a register of all patients receiving psychiatric care. Under this preliminary plan, all routine reports referring to the same individual will be linked by number to provide a record of his psychiatric experiences over long periods of time and involving different facilities. The register will provide minimum annual and long term estimates of incidence and prevalence by various demographic and socioeconomic characteristics and aid in the study of the results of psychiatric care, the flow of patients from one therapeutic resource to another, the reliability of diagnostic classifications, and the natural history of mental disorders. Negotiations to establish such a register are underway. It is hoped that this coordinated research can be undertaken in the near future.

In order to attain uniformity of register methods and definitions, the Biometrics Branch conducted the first meetings of the several groups in the country that have started, or are interested in starting, some type of register program. The Chief of the Section also visited the Monroe County, New York, register to observe the operating procedures of this register and to provide consultative services.

Study on Factors in Development of Emotional Disorder. A controlled retrospective study has been initiated with the Johns Hopkins University, to study some of the factors in early life that may be associated with the development of emotional problems in children. The study will use interviewing techniques and record search for data to test several hypotheses related to the role of feeding, toilet training, sex training, handling of agression and parental deprivation, in personality development. A number of studies have dealt with the area of early infantile socialization experiences. However, results have been equivocal and much of the methodology has been questionable. The present study will investigate the experience of a patient sample and a control sample of considerable size, and will attempt to avoid biases introduced by previous methodology.

Miscellaneous. Several publications of the Joint Commission of Mental Illness have made use of our data and analysis on professional staff and characteristics of psychiatric clinic outpatients, the authors indicating that this material is the only such data available in our country now.

A member of the Section served as a delegate to the White House Conference on Children and Youth.

A presentation by the Chief of the Section before a national conference of Chief Psychologists in State Mental Health Programs was accepted for publication in Public Health Reports. The Chief served as referee for a number of papers submitted for publication in Public Health Reports. She gave lectures and seminars on the epidemiological aspects of mental illness and on her research studies, at several universities. She was awarded a Degree of Doctor of Science in Hygiene, Johns Hopkins University School of Hygiene and Public Health; the research study in Maryland was accepted as her dissertation.

SECTION ON THEORETICAL STATISTICS AND MATHEMATICS

During the year the Section has continued to assist and consult with investigators on statistical, mathematical, and biometrical problems arising in various investigations carried out by the laboratory and clinical sciences at the National Institute of Mental Health as well as by scientists who are working in mental health problems outside NIMH. These services provide the scientists with the most efficient and valid statistical techniques available in the design and analysis of data.

The Section has given statistical aid to scientists at the NIH in a variety of disciplines ranging from physical chemistry through social anthropology, as well as providing liaison services between investigators in the laboratories and branches of the Institute, who collected large bodies of data, and the machine programmers of the electronic computer.

The Section has also been actively engaged in building deterministic and stochastic models in areas such as polymer chemistry, active transport, psychology and kinetics.

In addition to providing a variety of statistical and mathematical services to research and clinical investigators of NIMH, this Section has also been called into consultation by investigators outside NIMH. These services include consultations on the design of experiments, the analysis of data, the planning of sample surveys, mathematical models underlying data, and on statistical and probability theory.

Members of the Section have given seminars at several universities on statistics and mathematics and have given invited addresses at the Fourth Berkeley Symposium in Probability and Statistics as well as the annual meetings of various scientific societies.

Advice has been provided to various committees with regard to grants, surveys, and proposals in the field of mental health. Members of the Section have served on the Study Section for Accident Prevention, on the Medical Research Advisory Board of the FAA, and the Research Section of the Group for the Advancement of Psychiatry, reviewed manuscripts arising within the Institute, and served as referees on papers submitted for publication in statistical journals.

One member of the Section received a Ph.D. in mathematical statistics in June 1960. Another member was visiting associate professor at Iowa State University in the spring of this year. The Chief of the Section, who is currently visiting professor at Stanford University, was made a fellow of the American Statistical Association in recognition for his researches in statistical methodology and his high level consultation to scientific workers.

In addition, research in mathematical statistics in several different areas is being vigorously pursued.

Some examples of the investigations in which this Section has participated by providing consultations in design and analysis of data are:

1. Models for muscle membrane
2. Models in polymer chemistry
3. Ecological investigations in animals
4. Permeability properties of the blood-brain barrier
5. Size of extra-cellular space in the brain
6. Reaction time studies
7. Studies in Power and Authority
8. Self-concept in health studies
9. Speech phenomena in the psychotherapeutic hour
10. Infant behavior in the home and in a nursing home
11. Brain lesion studies in monkeys
12. Nerve regeneration in cats
13. Muscular contraction mechanism studies
14. Drug experiments in humans and animals
15. Studies in why students fail in college
16. Accident prevention studies
17. Factor analytic and principal component studies in social psychology
18. Calibration of methods of measuring blood pressure
19. Investigations of the dynamics of psychotic populations

OFFICE OF THE CHIEF OF THE BRANCH

During the year the Chief of the Branch engaged in certain activities that might be noted.

In February 1960 he completed a three months' assignment for the World Health Organization. He served as a consultant to the Mental Health Section of the WHO and to the Governments of New South Wales and Victoria (Australia), the Philippines, Taiwan, and Japan on the development and utilization of records from psychiatric institutions for research on the epidemiology of the mental disorders and on operational studies related to patterns of utilization of these institutions by the members of the population groups served by such facilities and the effectiveness of the services provided. A detailed report of the findings was submitted to the WHO for the use of the Mental Health Section in developing its program in epidemiology, and for use of the governments of the countries visited in developing national statistics concerning the care, treatment and rehabilitation of the mentally ill and programs of epidemiological research.

He also served as Chairman of the Subcommittee on Biostatistics of the Program Area Committee on Mental Health of the American Public Health Association. This Subcommittee completed drafting a chapter on "Data Collection and Analyses for Program Planning and Evaluation" for a manual on A Guide to Control Methods for Mental Disorders being prepared by the Program Area Committee on Mental Health.

The Chief continued his work with the Subcommittee on Classification of Mental Disorders of the U. S. National Committee on Health and Vital Statistics. This Committee is developing recommendations for revision of Section V (Mental, Psychoneurotic and Personality Disorders) of the International Statistical Classification of Diseases, Injuries and Causes of Death.

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19. Locke, Ben Z., Kramer, Morton, Pasamanick, B. Immigration and Insanity: First Admissions to State Mental Hospitals Among the Native-Born Population of Ohio at Mid-Century. Vol. 75, No. 4, pp 301-306, Public Health Reports, April 1960.

20. Locke, B.Z., Kramer, M., Pasamanick, B. Mental Diseases of the Senium at Mid-Century: First Admissions to Ohio State Public Mental Hospitals. American Journal of Public Health, Vol. 50, No. 7, pp 998-1012,July 1960.

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ANNUAL REPORT
COMMUNITY SERVICES BRANCH, NIMH
January 1, 1960 - December 31, 1960

Introduction

The major function of the Community Services Branch is to assist State and local agencies to improve, extend and strengthen their programs, for the promotion of mental health, prevention of mental disorders, and care, treatment and rehabilitation of the mentally ill. Community Services Branch staff provide a communication network for the dissemination of research findings and for feedback to the Institute on needs, problems and new hunches coming from the field of practice. The application of new research knowledge in everyday operating programs and experimentation with new methods and techniques is fostered and encouraged. A wide range of methods are used including: regular consultation with State and local programs, operation of demonstrations and pilot projects, Technical Assistance Projects, program analysis, operational, research and evaluative studies, surveys of State programs, and the administration of the Federal grants-in-aid and States Mental Health Project Grants programs. In the partnership of "research and development", the task of professional and technical assistance is "development."

The long range goal has been the development of a comprehensive range of mental health services available to people living in every part of the nation. Further the objective has been to move outmoded, traditional practice towards modern practice which applies recent knowledge from research. Innovation, the trying out of new methods and techniques, and the evaluation of both the old and the new is encouraged.

Federal Legislation and Appropriations

The total operating budget of the Community Services Branch for staff and administration in the fiscal year 1960 was $1,473,000. In fiscal year 1961, this amount increased to $1,688,000. The appropriation for the Mental Health Project Grants program (Title V, Public Law 911) was increased from $3.8 million in fiscal 1960 to $5.7 million. The appropriation for grants-in-aid to the States for community mental health was increased from $5,000,000. in fiscal 1960 to $6 million in fiscal 1961.

No major Federal legislation directly concerned with the operations of the Community Services Branch was enacted during this calendar year.

Branch Staffing and Administration

This year brought marked change to the Branch's staffing. At the end of 1960, one hundred and one positions were filled and twenty-five were vacant. Of these, seventy-one were professional positions and fifty-five were clerical positions. Nineteen positions were transferred from the Community Services Branch when the Mental Health Study Center was given Branch status within the National Institute of Mental Health. The fifteen vacant professional positions and ten clerical positions necessitated that recruitment continue to be an important and time-consuming activity. The benefits derived from the Career Development Program of the Branch were effectively demonstrated this year when two Regional Office positions were filled by personnel in the Career Development Program.

Federal Grants-in-Aid to States

Federal grants-in-aid to States increased from $4 million dollars in fiscal year 1959 to $5 million in fiscal year 1960 and to $6 million in fiscal year 1961. These funds were used for the promotion of mental health and the prevention of mental illness and for other community services, for the care, treatment and rehabilitation of the mentally disturbed, exclusive of inpatient care in hospitals and institutions. The increased allocation enabled the minimum grant to be increased from $25,000 in 1959 to $40,000 in fiscal 1961.

Only 22 States had state community mental health programs or plans when the National Mental Health Act was passed in 1946. In 1960, every State had an organized program providing help and leadership in the development of local community mental health services. Federal, State and local funds budgeted by State Mental Health Authorities for community mental health services increased to $65 million in fiscal year 1960 or an increase of 16.9% over the 1959 expenditures. The Federal grant-in-aid represented 9 percent of total funds budgeted by States in 1960 for community mental health services.

Approximately $6.5 million of the increase in 1960 was budgeted for the expansion of clinical and local mental health services. It was planned to use the remainder to expand State-level staff, research, demonstrations, and training.

Federal grant-in-aid funds have been used as "seed-money" to help establish mental health services in communities. As Federal funds have been freed from one local project, they have been utilized to initiate other projects.

Mental health consultation to other State agencies and to local communities regarding the incorporation of mental health concepts into these programs has been an effective means of extending both preventive and

therapeutic mental health services. Mental health education of the general public has also been a major endeavor. Pilot projects, evaluative studies and training have been endeavors begun with Federal funds and after such time as was necessary to demonstrate their value State or local funds have taken over.

The following excerpt from the New York plan for the use of the Federal grant-in-aid illustrates some of the imaginative ways that these funds can be used:

> "The percentage of National Mental Health Act funds supporting traditional and demonstrated types of community mental health services is steadily diminishing....."
>
> "Over two-thirds of the (grant-in-aid) funds available to New York State through the National Mental Health Act were used for the support of training centers for community service personnel and for pilot projects and demonstrations including:
>
> 2 day treatment centers for seriously disturbed children
> A learning disability center
> A demonstration and evaluation mental health project in selected schools in the city of Rochester
> An evaluation of an outpatient psychiatric service in a teaching hospital
> The utilization of a trained social worker to reduce early dropouts from rehabilitation service for discharged mental patients, and a demonstration of a school-connected mental health program in a rural county"

For fiscal 1961, the California Department of Mental Hygiene received requests for financial assistance from federal funds for 48 services. 11 are outpatient services; 11 family casework services; seven are for mental health education; seven psychiatric consultation; three therapeutically educational services for emotionally disturbed children; two rehabilitation services for the mentally retarded; six special projects related to mental health services; and a request for two training stipends in child psychiatry.

The request totalled $480,000 - more than is available from the federal allotment. According to the Director of the State Department ".....available funds - federal, state or local are not sufficient to the task."

Mental Health Project Grants (Title V)

The program of Mental Health Project Grants has continued to expand during the calendar year of 1960 not only in terms of the number of projects received and supported and in the amount of money allocated and expended, but, also, in the scope of coverage in terms of areas of investigation and increased geographic distribution.

Three basic approaches have been emphasized: (1) Improved hospital care and treatment; (2) improved administrative practices; and (3) improved community mental health programs. Special consideration has been given to projects aimed at these purposes when they pertain to critical areas such as alcoholism, aging, juvenile delinquency, mental retardation, or schizophrenia.

There has been increased interest in projects designed to promote knowledge concerning (1) modes of prevention and early detection of mental illness, (2) more effective and more economical alternatives to conventional hospitalization in a mental institution, (3) rehabilitation and reintegration of discharged patients into the productive life of the community, (4) encouraging interest and understanding in the community of mental health and mental illness, (5) better utilization of existing agencies and services, and (6) participation of personnel from other than the traditional mental health disciplines in the network of services for prevention, treatment, and rehabilitation.

Many of the projects are directed toward exploring new methods of treatment and techniques such as emergency service in the community at time of crisis, immediate service in outpatient facilities, day hospitals, half-way houses, psychiatric services in general hospitals, open hospitals, smaller units in mental hospitals based on the therapeutic community concept; and increased participation by general practitioners, nurses, social workers, and other skilled personnel in prevention, treatment, and rehabilitation programs.

The program of developmental grants which was begun in 1959 has been utilized with increasing effectiveness. These grants are usually for relatively small amounts of money and of short duration to permit an applicant to visit ongoing programs or to bring in expert consultation. These grants provide a mechanism through which the applicant can become informed, by personal observation, of new program trends and operations and can be encouraged to experiment with program changes. During 1960 support for 14 developmental grants was approved by the National Advisory Mental Health Council.

As a result of several requests concerning the support of applicants for brief periods of training in special areas such as the administration of mental hospitals, discussions were held with the Training Branch, NIMH, to determine the most appropriate mechanism for considering these requests.

Because of the responsibility of Title V for the stimulation of improved methods of hospital administration, it was decided that requests for brief and specific training were appropriate for consideration under the program of Mental Health Project Grants. During 1960 applications from 20 mental hospital administrators were approved for attendance at the Institute for Executive Development, conducted by the University of Chicago. Additional requests can be expected for brief training in specialized areas not only from hospital administrators but also from other groups with special needs, such as Judges of Juvenile Courts and police officers concerned with problems of juveniles.

As a result of Congressional Report on Juvenile Delinquency and the resulting allocation of funds to NIMH to stimulate project activity in this area, there has been increased attention given to delinquency by Community Services Branch staff. In cooperation with the Professional Services Branch and the Training Branch effective efforts have been made to promote projects that will contribute to better methods of prevention and control of delinquency. By the end of the calendar year 1960 there will be 16 projects in the area of juvenile delinquency being supported under Mental Health Project Grants with an additional 20 projects in this area awaiting consideration by the Review Committee in January of 1961.

In the calendar year 1960 applications for Mental Health Project Grants were received and processed as follows:

	Applications Received		Applications Approved	
Council Meeting Date	Number	Amount	Number	Amount
March 1960	73	$ 2,605,197.	25	$ 770,682.
June 1960	127	4,225,155.	53	1,130,402.
November 1960	86	3,395,511.	29	840,731.
Total, 1960	286	$10,225,863.	107	$2,741,815.
Total, 1959	243	9,372,298.	84	2,244,734.
Increase in 1960	43	$ 853,565.	23	$ 497,081.

At the Annual meeting of the American Psychiatric Association, twelve papers were presented which reported on projects supported by the Mental Health Project Grant program.

Ad Hoc Committee on Planning for Mental Health Facilities

During 1960 a representative of the Community Services Branch has participated on the Ad Hoc Committee appointed by the Surgeon General on Planning for Mental Health Facilities. This Committee composed of

representatives of the State and Territorial Mental Health Authorities and State and Territorial Hospital Authorities has completed a report designed to develop principles for meeting the Nation's growing need for more adequate mental health facilities. The Committee examined changing concepts in the care, treatment, and rehabilitation of the mentally ill and related these concepts to facility planning. The Committee developed planning principles which might be followed by States to implement the development of appropriate mental health facilities. The Committee report will be considered by State and Territorial Mental Health Authorities at the next meeting with the Surgeon General.

Technical Assistance Projects

Technical Assistance Projects have been developed through the past six years as an extension of consultation and technical assistance regularly provided to the States through the regional offices' and headquarter's mental health staff. In 1955 one project was held; in calendar year 1960 there were twenty-seven projects completed at a total cost of approximately $107,147. The average cost of technical assistance projects has been approximately $4,000.

This year Technical Assistance Projects were used by the States and the Branch as a method of exploring program needs and resources in many program areas. New areas included mental health in industry, delinquency, psychiatric in-patient units in general hospitals, services to geriatric patients, emotional problems of Indian students in boarding schools, and socio-legal problems in mental health. The following is a listing of the projects completed in calendar year 1960:

STATE	PROJECT TITLE
CONNECTICUT	The Partnership of Clergyman and Psychiatrist: Toward a Better Understanding and Integration of Their Respective Roles
MAINE	Community Mental Health Services
CONNECTICUT	Public Health Nursing in Mental Illness
MASSACHUSETTS	Mental Health Applications in Correctional Practice
PENNSYLVANIA	Creative Use of Mental Health Films
NEW HAMPSHIRE	Mental Health in the Schools
SOUTH CAROLINA	Working Together for Better Mental Health
GEORGIA	Joint Interests and Responsibilities of the Voluntary Association and the Public Agency in the Development of Community Mental Health Programs

STATE	PROJECT TITLE
MISSISSIPPI	Alcohol Education in Secondary Schools
KANSAS	Lay Leadership Training for Community Mental Health
NORTH DAKOTA	The Role of the Clergy in Understanding and Counseling the Alcoholic and the Family
MINNESOTA	The Role of Social Workers and Volunteer Directors on Community Planning for Psychiatric Patients
NEW MEXICO	The Secondary School in the Prevention of Alcoholism
WYOMING	Socio-Legal Problems in the Area of Mental Health and Mental Illness
CALIFORNIA	Planning for Alcohol Education
CALIFORNIA	Multidisciplinary Programming in Alcoholism Investigation
RHODE ISLAND	Bridging Public Health and Mental Health Programs - A Conference for Mental Health Nurse Consultants
MASSACHUSETTS	Nursing Care for the Alcoholic in the General Hospital Setting
PENNSYLVANIA	Mental Health in Industry
SOUTH DAKOTA	Planning Agency Participation in a State Alcoholism Program
TEXAS	Extending Clinic Services Into the Community
NEW MEXICO	Emotional Problems of Indian Students in Boarding Schools and Related Public Schools
IDAHO	The Role and Responsibility of the Probate Courts and the Idaho Department of Health in the Prevention and Treatment of Juvenile Delinquency
KANSAS	Education About Alcohol
HAWAII	The Use of Mental Health Concepts in Providing Patient Care

STATE	PROJECT TITLE
FLORIDA	Psychiatric In-Patient Units in General Hospitals
SOUTH DAKOTA	Services to Geriatric Patients

Hospital Consultation Services

Staff has worked with regional office and State staffs in planning for many aspects of mental health programs. This has included meeting with the Governor's Planning Committee in one State and with a Committee charged with the responsibility for developing standards for mental health programs in another State. In one State, consultation was requested to help plan better integration between the State mental hospitals, the county homes and local hospitals.

There is a continuing trend in the State mental hospital programs to achieve better integration between State hospital programs and other State and local agencies and facilities. This is particularly true in the field of aging. States are attempting to devise ways in which a person can get the care that he needs with the minimum of arbitrary restrictions resulting from legal or financial policies. There is also consistent interest in the States to treat the person outside the hospital where possible, and to coordinate the treatment efforts of the hospital and other community mental health facilities. The upgrading of staff through staff development approaches is evident throughout State programs. Title V projects have reflected and stimulated these trends.

The staff has put special emphasis on consultation with community agencies that may make a contribution in the area of juvenile delinquency. A number of Title V project requests have been stimulated in this area. This includes stimulation of new approaches to the problem of delinquency and of demonstrations in communities with unique problems, such as Puerto Rico.

Our philosophy of program development has been implemented also through participation in National conferences such as the White House Conference on Children and Youth, Planning Committee for the White House Conference on Aging, the Arden House Seminar on casework with older people, the National Nursing Home Conference, and the Institute in Executive Development for Psychiatric Administrators.

Surveys

The Hospital Consultation Service completed two surveys during 1960. The North Dakota survey was requested by the Legislative Research Council of North Dakota, which had been directed by the North Dakota Legislature to make

a study of present mental health facilities and to develop a plan for the future mental health program in North Dakota. The Public Health Service was asked to assist the State in this study and to formulate recommendations for the mental health program in North Dakota. The survey team visited the major mental health facilities in the State and met with officials of those State agencies responsible for various mental health functions and activities. The survey team also visited the State University, State College, and two teachers colleges, and conferred with local health and welfare officials, general practitioners, juvenile judges, and officials of voluntary agencies and groups. Conferences were held with the representatives of the Indian Health Service area office and the staff members of the Kansas City Regional Office of Department of Health, Education, and Welfare concerning health and welfare programs in North Dakota. The preliminary findings and recommendations were discussed with the Subcommittee on Government Organization of the Legislative Research Committee and the final report was discussed at an open hearing sponsored by the Legislative Research Committee.

The survey team has met with a universal response of helpfulness, interest, cooperation, and concern about the problems of the mentally ill in North Dakota. There is ample evidence that the citizens of North Dakota are desirous of improvement and expansion of the mental health program in the State.

The survey of the Medical Center for Federal Prisoners at Springfield, Missouri was requested by the Director of the Bureau of Prisons to be used by the Bureau in its long and short-range planning for psychiatric care of mentally ill prisoners. The National Institute of Mental Health was asked to study the psychiatric treatment available at the Medical Center for Federal Prisoners at Springfield, Missouri and the problems of psychiatric treatment in the Federal Prison System. Visits were made to the Medical Center and to other Federal Prisons in order that team members might become familiar with the total prison system and its problems. Several conferences have been held with the Headquarters staff of the Bureau of Prisons to discuss recommendations of the survey and to provide continuing consultation to the Bureau. A special meeting was arranged for psychologists working in prison hospitals to discuss training and research.

Near the end of the year, work was underway on a survey of the mental health program and facilities of the Virgin Islands.

Police Training Film

A new venture, the production of a training film for police officers, was completed during the year. BOOKED FOR SAFEKEEPING is a 33-minute, 16 mm. sound film which shows police officers how to handle severely disturbed persons whom they must apprehend.

A great many people who suffer serious mental disturbance are in the hands of the police before they reach the hospital. The way they are handled during this critical period can have a far more important influence on their chances of recovery than is generally realized. Handling of the mentally ill is one of the most difficult of all problems for the police, and they are very interested in improving their methods.

The degree of police concern with this problem is evidenced by the widespread use of the manual How to Recognize and Handle Abnormal People, prepared in 1952 by the Louisiana Association for Mental Health. Over 60,000 copies were sold, and the manual has now been revised and reprinted. Dr. Loyd W. Rowland, Executive Director of the Association, and one of the authors of the manual, was the first to suggest the desirability of a film.

After extensive inquiry among police chiefs around the country, contractual arrangements were made with the Louisiana Association for Mental Health for the production of the film. George C. Stoney, an outstanding producer of educational and health films, was brought in to do the actual writing and directing. New Orleans Police Department cooperated fully - 18 of its officers playing the principal parts in the film.

Several teaching points are stressed: The importance of correct police procedures, the fact that time is a great factor in quieting the excited person, the necessity for reassurance and consideration, progressive release from restraint, and avoidance of deception. The general theme of the picture is: treat every person as if you are to handle him again, as indeed you may!

With the increasing use of drug therapy and early release from the hospital, it is inevitable that police will have repeated contacts with a sizable number of persons. Aside from those they will have to reapprehend, the police will have an increasing opportunity to play a supporting and sustaining role in helping released patients maintain themselves in the community. The potential role of police as future "mental health workers" in the community has hardly been explored as yet, but may prove to be extensive. In any event, there is every indication that future training of police officers will include a greatly increased emphasis on mental health.

Aside from its use in police training, the film will bring home to communities the necessity for improved facilities for immediate care of disturbed persons. In most of the United States, emergency handling means jail, - anywhere from a few hours to several days or longer. The film does not show ideal physical conditions for the care of the mentally ill, but rather the realistic conditions which exist in most communities. The police are shown as doing the best they can with what is available, using humane and effective methods, but working under handicaps which the community could correct.

The film will be available on a loan basis, without cost, to any police department or law enforcement agency in the country, and also to health

agencies and associations. It is expected that many of the latter will want to purchase prints of their own, and these can be made available at the very low cost of $70.

The film has been previewed extensively by leading police and law enforcement officials as well as by those in the mental health professions. Special advance showings were made at the annual meetings of the International Association of Chiefs of Police in Washington, D. C., and the National Association for Mental Health in Denver, Colorado. When the film is released, with the discussion guide now being prepared to accompany it, there is every indication that it will be widely used.

Public Assistance and OASI

The Bureau of Old-Age and Survivors Insurance sponsored a conference to discuss trends in treatment of the mentally ill as related to the policy of the Old-Age and Survivors Program. This conference was the outgrowth of a series of discussions between Community Services Branch Hospital Consultation staff and OASI staff. The OASI staff has been concerned about how social security benefits were being made available to, and being used for, patients in mental hospitals. The special consultants brought in for this conference included selected mental hospital administrators, state welfare directors, mental health commissioners, and business administrators.

Major issues emphasized were the problems in the determination of when a patient was not capable of managing his own benefits and in deciding whether a family member, a friend, or the hospital should be the representative payee. The principal was enunciated that it was more desirable for someone other than the hospital to be the representative payee. It was pointed out that this would promote continuity of arrangements in view of the shorter terms of hospitalization. It was also indicated that, whenever possible, the patient should continue to receive his own benefits. There was agreement that hospitals should not expect to be reimbursed from Old-Age and Survivors Insurance funds at a higher rate than they are from any other funds that the patient might have. It was also indicated that more attention should be given to the certification by the doctor of the patient's capacity or incapacity to manage his benefits.

The proceedings of this Conference will be used by the Bureau in the development of future policy. The proceedings have also been made available to our regional offices. The Bureau staff plans to discuss with us the policy changes that will be made.

Several discussions have been held with the staff of the Bureau of Public Assistance regarding the availability of public assistance benefits to mentally ill patients. The recommendation of the State and Territorial Mental Health Authorities, that the provision in the Social Security Act excluding mental patients should be eliminated, has been the major focus of

these discussions. The Bureau staff has also discussed with us the possible benefits and limitations of benefits that will be available to mentally ill patients under the 1960 revisions to the Social Security Act. The issues involved in the availability of public assistance and OASI benefits for mentally ill patients were discussed with both the State and Territorial Mental Health Authorities and the State Chief Social Worker in Mental Health. Programs.

Alcoholism

Central and Regional Office consultation to State and local agencies continued to increase during the year. In the past six months, the Consultant on Alcoholism met with the mental health consultants at six of the Regional Offices to discuss alcoholism program planning. Activities underway in each State of the Region were reviewed. Consideration was given to alcoholism services in local health departments, to admission of alcoholics by more general hospitals, to more acceptance of alcoholics in the population being served by mental health centers, to consultation to social agencies by personnel in alcoholic clinics.

Eight Technical Assistance Projects on alcoholism were supported. They were: "Planning for Alcohol Education" (California), "The Secondary School and the Prevention of Alcoholism" (New Mexico), "The Role of the Clergy in Understanding and Counseling the Alcoholic and the Family" (North Dakota), "Alcohol Education in Secondary Schools" (Mississippi), "Multidisciplinary Programming in Alcoholism Investigations" (California), "Planning Agency Participation in a State Alcoholism Program" (South Dakota), "Nursing Care for the Alcoholic in the General Hospital Setting" (Massachusetts), and "Education about Alcohol" (Kansas).

The mental health consultants in Region IV (Atlanta) arranged the third annual two-day meeting for State-level alcoholism program personnel in that area.

The mental health and the public health nurse consultants in Region VI (Kansas City) attended the 1960 Yale Summer School of Alcohol Studies. The School was assisted again by providing the services of three resource personnel so continued emphasis could be placed on the public health aspects of alcoholism as well as upon epidemiologic research. The one-week Schools of Alcohol Studies in Mississippi, North Dakota and Utah were assisted in giving more attention to education about alcohol, to pastoral counseling of the alcoholic and his family and to public health aspects by providing the services of our staff or of other resource personnel. Three-day conferences on alcoholism in Colorado and in Texas were aided in a similar way.

The special research grant concerned with behavior, including alcoholism, of a tri-ethnic population is in its second year. The study, conducted by the University of Colorado, seeks to gain information helpful in developing more effective approaches to Indian mental health. It was reviewed

recently with the Division of Indian Health personnel. The interests and needs of American Indians relative to alcoholism are getting increased attention in some States (e.g. New Mexico and North Dakota).

Some State and local agencies, which have been concerned primarily with care and treatment of the alcoholic and his family, have requested and received consultation about a possible broadening of their functions. For example, the Florida Alcoholic Rehabilitation Program wants to develop more consultation services by local alcoholism clinics to social agencies. The Adult Guidance Center (for alcoholics) of the Mental Health Service, San Francisco Department of Public Health, has been interested in developing consultation services to staff of the nine health centers of that Department.

The tuberculous alcoholic patients are receiving considerable attention. Community Services Branch staff have reviewed this problem with personnel of the Washington office of the Communicable Disease Center. Consultation has been provided to State health and other agencies. For example, the Massachusetts Department of Public Health has conducted a study of the tuberculous alcoholic and is considering setting up a demonstration project.

Community Services Branch staff continued to share information and ideas with the National Council on Alcoholism, the National Tuberculosis Association, the Industrial Medical Association, various religious groups and educational associations.

Assistance was given to the Publications and Reports Unit, NIMH, in the preparation of a popular leaflet "Alcoholism" which has been given wide distribution.

Alcoholism Demonstration

This NIMH demonstration which began in July, 1959, functions as an integral part of the Mental Health Bureau of the Prince Georges County, Maryland, Health Department.

The Mental Health Bureau has as its director a clinical psychiatrist working with a professional staff of two psychologists and two psychiatric social workers. The Alcoholism Demonstration brings to the staff an additional psychiatrist, psychologist, and a psychiatric social worker, as well as a mental health nurse consultant.

The three broad purposes or objectives of the Demonstration are seen as: (a) rehabilitation of the alcoholic and his family through the combined efforts of appropriate community facilities (b) development of an educational and preventive program (c) evaluation. Underlying these three objectives are the goal of developing activities appropriate to a "public health approach."

In the rehabilitation program, there has been considerable clinical activity. The part of this activity pertinent to a public health point of view centered on the development of three aspects other than direct patient-therapist contacts. These are:

1. Development of relationships with referral sources

Working relationships have been successfully achieved with the Prince Georges General Hospital, the Spring Grove State Hospital and the clergy in the County.

The majority of alcoholic admissions to the psychiatric wing of the Prince Georges General Hospital are seen by the psychiatrist of the alcoholic clinic. Clini services are explained; information valuable for both diagnostic and research purposes is gathered.

The alcoholic clinic is notified of every alcoholic discharged from the Spring Grove State Hospital who is a resident of Prince Georges County. The patient is informed by mail or telephone of the Clinic, and if he does not come, a public health nurse visit is planned.

One attempt to develop relationship with one group of community "caretakers" was notably successful. This was with the clergy and done through a luncheon interfaith meeting attended by over forty clergymen from throughout the County.

2. Development of a meaningful family approach

The family is taken into the program. Referrals are almost as frequently from relatives as from patients. Of the therapy groups, at least one is of spouses and other relatives. Proposed next steps center heavily on this area. A plan is being worked out to determine the feasibility of utilizing the school health program and its case-finding of children with health problems, as a means of locating families where alcoholism plays an important role. Conversely, it is planned that the public health nurse will visit families of alcoholics to identify other health problems especially among children.

3. Utilization of Health Department resources

Developing meaningful working relationships within the Health Department between the Bureau of Mental Health and Bureau of Public Health Nursing has occupied a large portion of staff effort and planning. Appropriate policies of referral from the general caseload of public health nurses to the Mental Health Bureau have developed. Conversely, the Mental Health Bureau called upon public health nurses for home visits to (1) cases of alcoholics in treatment (2) alcoholics who do not show up after being referred (3) alcoholics or relatives who break appointments.

Approximately twelve public health nurses attended an inservice training program during the past year which has led to plans to continue and increase this activity. There is a bi-monthly staff meeting where public health nurses present cases of alcoholism they have seen either in their general caseloads or on referral from the alcoholic clinic.

Other Health Department personnel, notably the nutritionist and health educator have been utilized. The nutritionist plans to offer consultation to both patients and public health nurses.

As part of the development of an educational and preventive program, several pamphlets describing the services have been developed and widely distributed throughout the County. Contacts via talks and meetings, such as with clergymen previously discussed, as well as similar meetings with physicians have taken place. The evaluation of the significance of these efforts is difficult to determine. For instance, an exhibit at the County Fair describing the program was seen by thousands of citizens. As far as can be determined, not one single referral came through the clinic as a result of this exhibit.

To carry out the objective concerned with evaluation, two members of the Mental Health Study Center staff, a psychiatrist and mental health nurse, serve as resource personnel to the Health Department in the area of evaluation. A series of planning meetings led to the development of a data gathering instrument to be used by the public health nurse, psychiatrist, social worker, and other staff in gathering data on alcoholics and their families. The newly acquired statistician, recently employed by the Health Department, has been helpful. One of the primary goals has been to design a practical instrument feasible for use by other health departments. If the gathering of this research information can be carried through successfully, many of the original questions that formed basic objectives will be not only answered but elaborated upon. For example, it will be possible not only to answer the questions "of those persons with alcoholism who are reached, how many accepted services in whole or in part?" - but hopefully to describe significant personal and sociological differences between those who have accepted treatment and those who did not.

The Drug Addiction Demonstration Center

The Demonstration Center in New York City was established in 1957 as an experimental project to refer selected dischargees from the Public Health Service Hospital in Lexington, Kentucky returning to New York City to appropriate community agencies for rehabilitative help, to assist community agencies to offer services to drug addicts, and to continue a longitudinal study of patterns of relapse and certain aspects of the community adjustment of a sample of dischargees from Lexington. Through consultation and informational service, the Center attempts to broaden the community understanding of the special needs of discharged addicts.

The Center is staffed by a Director (social worker), a case work supervisor, six social workers and a psychiatric consultant. Members of the advisory committee represent a number of City and State health and welfare agencies concerned with problems of drug addiction.

To date, a substantial number of referrals has been made to several employment services and the New York City Department of Welfare. Through the efforts of the Center, the policies of these agencies have been modified and services extended to addicts referred by the Center. Only a small number has been referred to family agencies and mental hygiene clinics. The staff is currently endeavoring to develop techniques for locating and referring a larger number of suitable patients to these agencies.

Through a casework relationship, workers at the Center and other agencies have been able to help a number of addicts abstain from use of drugs for increasing periods of time. At the beginning of the year, a series of seminars was held with representatives of family agencies which had accepted referrals of Center patients in order to help them compare their experiences and increase their understanding of the addict group. The meetings served to clarify a number of questions troubling them and allay their anxiety about working with addicts. Agency workers were also helped to view relapse more dynamically and to accept the idea of working with patients who were using drugs irregularly.

In cooperation with the social service staff at Lexington, the Center has begun to work with patients' families in order to prepare them for the patients' return. The Center staff has come to consider addicts less as unattached persons and more as members of family groups. There has been a growing awareness, also, of the differences in working with middle class patients and those of lower socioeconomic groups; and the need to elucidate the cultural factors predisposing members of Negro and Puerto Rican populations to drug use. Workers are further learning to modify techniques used with other patients, leaning more heavily on such approaches as: extending service in crisis situations, revising customary concepts of fixed time schedules, and limiting goals with these chronically ill patients.

The Center has continued to function increasingly as an informational and consultative resource, answering inquiries by the interested lay and professional persons. Its influence has been extended through consultation with community agencies, participation in public conferences and seminars, and membership in municipal and voluntary committees interested in formulating programs for the management of addiction. Papers written by the staff have been published and may serve to encourage work with addicts.

Mental Retardation

Consultation and technical assistance from Central Office and Regional Office staff members, in the area of mental retardation, continue to be important in terms of time and priorities. Increasing amounts of grants-in-aid

to States' funds are being devoted to mental retardation. Two technical assistance projects, relating to mental retardation, are presently in the planning stage.

Under the program of Mental Health Project Grants, the Community Services Branch is able to support demonstration, experimental and pilot studies related to the care, treatment, and rehabilitation of the mentally retarded. Projects have already been completed in administrative and record keeping, and treatment aspects of the program for retarded children. Among projects currently being supported are the following: a language development program for mentally retarded children, a program for preschool retardates and parents, interdisciplinary investigation of learning disorders, collaborative management of mental retardation, an occupation day center for mentally retarded young adults, and use of public health nurses in a retarded children's program.

School Mental Health

The school mental health activities of our staff during 1960 group themselves into: (1) national level projects; and (2) technical assistance to States.

Several projects of national significance and scope were launched or continued this year by the headquarters consultant on school mental health. In cooperation with the Council of Exceptional Children of the National Education Association, a study of classroom process in current special class programs for emotionally handicapped children has been developed. Such a study will require both mental health and educational competencies in order to describe the operative psycho-social factors. The study is needed as a guide to future class development and teacher preparation, as well as to stimulate more definitive research.

At the request of the Education Branch of the Bureau of Indian Affairs, U. S. Department of Interior, the school mental health consultant visited reservations and Bureau schools in five States to study possible revisions of education programs to meet the needs of culturally deprived and emotionally disabled Indian children. Approximately a month was spent in observation to prepare for an on-going consultative relationship with the Bureau's Washington education staff.

Other important projects included:

1. Organizing a conference on methodology, terminology and research problems for NIMH research grantees working on school mental health problems.

2. Fostering the development of a joint mental health authority, school of education, and State Department of Education project for training

school superintendents and their staffs in the mental health aspects of school administration. (Maryland)

3. Developing plans for a "community laboratory" program of studies on the prevention of school behavior problems, drop-outs, and delinquency. (Quincy, Illinois)

4. Aiding the Professional Services Branch, NIMH, in developing a demonstration of a teacher-manned residential school for emotionally disturbed children. (Kentucky and Tennessee)

5. Drafting and implementing plans for a nationwide series (goal of 5,000 meetings) of local conferences of parents, teachers, and resource persons on "child guidance."

6. Consultation with the Training Branch, NIMH, and two leading schools of education re developing pilot studies to determine the best ways to train teachers for emotionally disturbed children in hospitals, training institutions, and public school special classes.

The school mental health research utilization projects begun previously were continued; including abstracts for the regional consultants' notebooks, a listing of all Federal school mental health related research in progress, and two more NIMH-Curriculum Development Research Conferences. New plans were implemented to disseminate the findings of the NIMH supported Banks Street College of Education project on the psycho-social impact of the classroom experience. The monthly liaison visits to the U.S. Office of Education and NEA have continued to expedite joint efforts to promote research, pupil personnel staff collaboration, and teacher training objectives.

Continued interpretation of mental health in education issues were made at national meetings of the American Association of School Administrators; the American Education Research Association; the Association for Supervision and Curriculum Development; the American Association of Health, Physical Education, and Recreation; and the Instructional Conference of the National Education Association, as well as through writings. Consultation was provided to educators or mental health personnel in fourteen States by the national consultant. A booklet prepared by the consultant on "Mental Health Programs for Local Parent-Teacher Associations" was given country-wide distribution by the National Congress of Parents and Teachers. It is estimated that some 3,500 meetings on mental health topics were held in local parent-teacher associations this last school year.

The School Mental Health Demonstration

Since November 1, 1959, this Community Services Branch demonstration has been carried out through a contract with the Florida Department of Health. The new staff now consists of a psychologist and a mental health nurse who

are State employees. The current objectives of the project are: (1) acquainting the public and private agencies and groups in the county with the purposes of the Demonstration (2) developing the role of consultant to those agencies in the county which give educational and technical services to children (3) exploring methods of in-service education with public health nurses and school personnel.

In the course of orienting other agencies about the Demonstration, contacts were made with the courts, the welfare department, the county ministerial association, the Business and Professional Women's Club, etc. As a result of these contacts, the courts called upon the Project staff to consult on cases. The Welfare agencies cooperated in joint planning for children known to project staff. Several ministers asked for consultation regarding counseling of church members.

Community agencies and groups expressed a strong demand for clinical services and it was difficult to communicate the idea that a major objective of the Demonstration is prevention and education.

In connection with the objective of becoming consultants to the school staff, a series of conferences were held with the Superintendent, instructional supervisor, pupil personnel director, school principals and health coordinators (teachers). As a result of these conferences, there were a number of requests from the administrative staff of the schools to confer about pupil problems as well as staff problems. With this group also, there was expression of demand for clinical services. Also it became evident that school staff have difficulty in using cumulative school records and information about students which is obtained through the county-wide testing program.

In-service education sessions were held with the public health nurses, the county mental health worker and other health personnel. The public health nurses continued to have difficulty in finding the time to devote to the Demonstration because of their many other duties. The project tried to help the nurses to integrate the teacher-nurse conference as part of their regular contacts with schools.

Regular in-service sessions were also held at the three schools participating in the Project. As with the public health nurses, a major obstacle was the lack of teacher-time to devote to the new mental health service. Usually the meetings were held after school.

In working with the faculty of the three project schools, the staff have described a general pattern which seemed to have been followed by each faculty group:

> The <u>first</u> phase could be described as getting acquainted with the project staff and with themselves.

The second phase: talking about their pet cases, their pet peeves, and personal problems.

The third phase, teachers begin to help other teachers talk about pupil problems and explore ways of dealing with them.

The fourth phase: with considerable cohesiveness, teachers discuss acute day-by-day problems.

Program Research and Evaluation

During the year an additional clinical psychologist joined the Program Research and Evaluation Section on a full-time basis. Planning was instituted for expanding consultation resources available in program research and evaluation. The general goal is to undertake a continuing critical review of present activities in both program and university settings, and to prepare effective guidelines for use in consultation. These materials will probably include a comprehensive book in addition to other briefer and interim publications. More detailed planning and a survey of existing activities were underway at the close of the year.

Program Analysis

Two major reports were completed during the year under the aegis of the program analysis staff. The first was a report of a study of the mental health education activities of nine State community mental health agencies, one State mental health authority in each region of the country.

The organization, program, and goals of mental health education of the State Mental Health Authorities were studied. While generalizations can not be made for the country as a whole, certain common patterns were noted in the States that were visited. Only a few of the State agencies had specialized mental health educators. Those serving as mental health educators were most frequently social workers by training. It was found that a considerable number of other agencies, both public and private, carried out mental health education activities in addition to the State agency.

Programs could sometimes be differentiated as having a mental illness or mental health focus. Those focusing on mental illness carried out such activities as informing the public about facilities, conveying information about the characteristics of mental illness and its treatment, consulting with "caretakers" and "gatekeepers" about early identification and methods of handling the mentally ill. Programs focusing on mental health were active in adding to the public's information about normal growth and development, about the characteristics of interpersonal relationships and conflict, about

prophylactic techniques for the resolution of tensions and the reduction of stress.

Among the educational methods, the mass media (newspaper, radio, television) were used for the dissemination of information about programs and facilities. Pamphlets and films, as part of a series of presentations to a specific group, were popular. The use of consultation with "gatekeeper" and "caretaker" groups was frequently pointed to as the most effective educational method. There was little organized research into the effectiveness of methods.

The second report was "Children of the Caribbean" - A Report on the Second Caribbean Conference for Mental Health. With the help of a special writer employed by the Publications and Reports Section, NIMH, program analysis staff prepared this book as a type of technical assistance to the Puerto Rico and Virgin Islands mental health programs who asked for the help. The book contains major papers by such persons as Dr. Erik Erikson, Dr. Milton J. E. Senn, Dr. Vera Rubin, and Dr. Fritz Redl, as well as background papers from representatives of the Caribbean Islands. The material in the book on the cultural aspects of the mental health of children should make the report of interest and significance outside the Caribbean.

During the year, a classification system was developed for coding, storing and retrieving published mental health materials. The activity is considered as a pilot project which will be tested and assessed before eventual conversion to electronic business machine equipment. Already a card file with several thousand entries is available. Next steps involve the integration into the system of data in staff trip reports and in the State plans for community mental health services.

Program analysis staff have also served as liaison to a similar pilot project developed and conducted by a committee of Regional Office Mental Health Consultants and focused on the needs of the regional offices.

For the first time, detailed guide lines were issued for the preparation of the annual State summaries describing the State community mental health programs. A procedure for clearance by States of these reports was initiated so that these very valuable descriptive reports can be distributed outside the Public Health Service. Eventually it is hoped that these reports can be issued as a regular publication.

Annual reports from the mental health sections in the regional offices was another innovation this year. Primarily intended for internal staff use, the first year's reports have already proved to be so valuable that they have been made required reading for Community Services Branch staff before visiting a regional office.

An article prepared jointly by the Branch chief and program analysis staff, "Next Steps in Community Health Programs," has proved to be unusually popular. Originally published in a report of the Northeast State Government's

Conference, the article has been reprinted in two other journals, "Adult Education" and "Pennsylvania Welfare."

Regional Office Activities

Mental Health Consultants in regional Offices continue to represent a major link between the National Institute of Mental Health and the State and local mental health programs. The Regional Office Mental Health Consultants provide information and assistance to mental health programs in helping them to utilize effectively the resources of the Community Services Branch as provided through Professional and Technical Assistance, Mental Health Project Grants, and Grants-in-aid to States.

As a result of continuing visits and consultation with mental health agencies, information regarding new trends, developments in programs is transmitted between the National Institute of Mental Health and operating services. Such reports highlight state, regional and national developments.

The Regional Office Staff report a redistribution of their own time and efforts. As State mental health programs mature, the Regional Office Staff find that their technical consultation is offered increasingly through conferences attended by representatives of state mental health authorities and other professional and citizen leaders of the state. The most frequent topics are aging, drug addiction, research and statistics, rehabilitation services, accident prevention, civil defense, juvenile delinquency, mental hospitals follow-up services, public health-mental health, alcohol, children's psychiatric care, clinics, mental health education, mental retardation, school mental health, community organization of mental health services and professional participation in mental health services. Of course a major method of consultation on program and administration continues to be conferences with representatives of the state mental health authority only.

Surveys are taking an increasing portion of the time and efforts of the Regional Office Personnel. The Regional Office Staff now report more and more involvement in mental hospital programs. This is occurring especially in relation to Title V applicants and grantees.

The Regional Office Staff are also reporting more frequent planning for joint efforts with regional offices of national voluntary health, welfare and education agencies. Within the Public Health Service Regional Offices, the Mental Health Section personnel are entering into joint planning with Special Health Services in regard to chronic diseases, research, aging and tuberculosis; with Hospital Facilities in regard to psychiatric units in general hospitals and in mental health clinics; with Children's Bureau in regard to mental retardation, foster care, emotionally disturbed children, juvenile delinquency and homemaker services; and with the Office of Vocational Rehabilitation in regard to the rehabilitation of the mentally handicapped.

1960 White House Conference on Children and Youth

Several members of the Branch Staff provided assistance to the White House Conference on Children and Youth. One staff member was assigned full-time, as coordinator of Studies of the White House Conference on Children and Youth, with responsibility for planning and producing a number of publications. The Coordinator of Studies developed and wrote "Prospectus on Research" as well as editing "Children and Youth in the 1960's" and "Supplement to Reference Papers on Children and Youth." He also directed the production of "The States Report on Children and Youth."

The Conference emphasized the need for a comprehensive approach to children's problems. It urged the integration of research and service. Such integration was seen as having significant effects on professional education, staff training, and organizing and structuring agencies. The need for expanded program research and evaluation was stressed. The need for increased manpower made personnel studies a high priority area. Improved manpower utilization was seen as a goal of training research, and evaluation.

1961 White House Conference on Aging

The Branch staff in both central and regional offices participated in a variety of ways in the organizing, planning, and development of this Conference. Staff members from the central office participated in three technical panels: (1) community organization, (2) social services, and (3) family life, family relationships and friends. The panels produced background publications in each of these areas for use in pre-Conference and Conference activities. In addition, the Branch assigned one professional person to work full time on the Conference staff in charge of planning for the Conference.

Conference of Chief Psychologists in State Mental Health Programs

The Tenth Conference of Chief Psychologists in State Mental Health Programs with staff of the National Institute of Mental Health was held in Chicago, Illinois, August 30-31, 1960. This Conference had a record attendance of 90 psychologists from 45 States, the District of Columbia, the Province of Ontario, Canada, the Southern Regional Education Board, the U.S. Army, and the Public Health Service. PHS participation came from two Bureaus, two Institutes of the National Institutes of Health, and three Branches of the National Institute of Mental Health.

Discussion centered around the following areas of concern: (1) more adequate graduate training in psychology through increased congruence between academic and practicum experiences to meet needs for research, training, administration, (2) behavior modification methods (including consultation and operant conditioning), (3) the maintenance of personnel standards (4) the

value of collaborative efforts between limited psychological resources in a State regardless of the organizational structure of its mental health program; and (5) ways of increasing the competitive position of State and local mental health programs in recruiting and retaining qualified psychological personnel. In addition to reports on current developments in State psychological services, special reports were made on NIMH Grants, NIMH programs in alcoholism, juvenile delinquency, and outpatient clinic statistics; on a National Institute of Neurological Diseases and Blindness study of conditions of pregnancy which forecast mental deficiency; activities of the American Psychological Association in accrediting practicum agencies and the work of its Committee on Mental Health Research and Programs; post-doctoral training for psychologists in Schools of Public Health; and a progress report on a Rural Mental Health Project in New Mexico.

Conference of Chief Social Workers in State Mental Health Programs

The 12th Annual Conference of Chief Social Workers from State Mental Health Programs was held on February 22-24, 1960, in Chicago, Illinois. This was one of the largest and most successful of all of the Annual Conferences of this group. There were approximately 79 people in attendance from 38 States and Puerto Rico. The general theme of the Conference was "New Approaches to Mental Health Problems." Among the subjects presented and discussed were "The Use of Research," "Screening for Pre-Admissions," "The Use of Regional Consultants in Community Mental Health Programs," and "Training Programs for Recruitment and Retention of Staff."

Miss Harriett Rinaldo of the Veterans Administration Central Office, Social Service Division, presented a paper on "Social Work Classifications and Standards." This paper touched on a number of critical problems faced by the State agencies interested in recruiting personnel, providing appropriate salaries and professional advancement opportunities.

Community Services Branch staff presented some of the highlights of community mental health programs as they are developing throughout the United States and Training Branch staff gave a report on "The Status of the National Institute of the Mental Health Training Program in Social Work." In addition to this, Community Services Branch staff led a discussion on "Current Consideration of Provisions in the Social Security Act Affecting the Mentally Ill."

Conferences of State Mental Health Nurses

Two conferences of State mental health and psychiatric nurse consultants were held during the year. The first took place on October 16, 17, 1960, in Salt Lake City, Utah, prior to the Mental Hospital Institute.

The first day was given to a meeting of State nursing consultants; the second, to a general meeting for nursing personnel in psychiatric situations. Of interest on the second day was the attendance of a fairly large number of psychiatric aides. All levels of personnel were encouraged to enter into the discussions. If psychiatric aide attendance at such meetings continues, it will be important to develop part of the program to meet their special needs as well as to include them in the general program for improving the nursing care of the mentally ill.

The second conference was held in San Francisco, California, October 29-30, 1960, before the meetings of the American Public Health Association.

For the third consecutive year, a report of "Mental Health and Psychiatric Nursing Activities in State and Local Mental Health Programs," was prepared and made available to State consultants, advanced psychiatric and mental health nurse program directors, and regional nursing consultants. The material in this report serves as an information guide on new developments in State programs involving nursing personnel, as a source of resource material for students in advanced programs, and as a source for resource personnel for Institutes and workshops for universities in advanced programs planning short courses.

Since this was the first meeting held in the far West, it attracted a considerable number of people who had not been able to attend meetings held in the East. An innovation at this year's meeting was the use of case materials for discussion in the small group meetings.

The Community Services Advisory Committee

The Community Services Advisory Committee met on April 4 and 5, 1960, at the Stone House, National Institutes of Health, Bethesda, Maryland. The Committee considered ways of implementing the Congressional mandate for increased activity in social program areas - particularly in the areas of aging, alcoholism, and juvenile delinquency. This also brought consideration of the kinds of demonstrations and pilot projects needed, means of providing services in view of the shortage of mental health manpower.

The Subcommittee on Rural Community Mental Health reported to the Committee as a whole. A crucial problem in the development of rural mental health programs is the serious manpower shortage and accentuated by problems of retaining experienced personnel in rural areas. There is need to develop more collaboration with public health, agricultural, educational, welfare, religious, medical, legal, economic, family and other community agencies and organizations in rural areas so as to benefit by their long experience in working in rural areas. As in urban services, financing, development of standards, development of relationships, and administration were areas needing special attention. Also basic to further planning of rural community mental health services would be surveys or other methods of collecting

descriptive data. Such data would be helpful in a comparative study of rural and urban community mental health services. It could also aid in answering questions as to whether special training would be necessary for people who are to work in rural areas.

Discussion also focused on the rural community mental health role of a local general hospital and of local welfare departments in the 500 counties without basic health programs. The role of the general practitioner was also viewed as of paramount importance in rural mental health agencies. The Committee agreed that the Community Services Branch might act as a catalyst in crystallizing interest of State groups in exploring rural community mental health needs and services.

The Subcommittee on Training Community Mental Health Personnel also reported to the Committee in plenary session. It reported that the present training programs have been concerned with training the specialist primarily for academic careers, for private practice oriented to treating individual patients, rather than for community practice. Many misgivings exist as to whether there is enough solid content to develop substantial training services in relation to community mental health. Questions were raised about the need for clinical training of all community mental health personnel.

Another problem was seen in the lack of applications for training submitted by qualified candidates. Of the approximately 4,000 mental health stipend recipients trained between 1948-1958, 48 percent are engaged in some type of public service. Yet very few are engaged in community mental health programs on a full-time basis. This information led the Committee to review approaches to training community mental health personnel such as that of the Harvard School of Public Health, Columbia University, Pittsburgh School of Social Work, Stanford University, University of North Carolina and non-academic programs in Quincy, Illinois; Sioux Falls, South Dakota; Louisville, Kentucky; as well as the Prince Georges County Mental Health Study Center Training Program. Because of the lack of formal academic training in regard to community mental health, in-service training has and is playing a vital role in the evolution of community mental health services.

Conference of State and Territorial Mental Health Authorities

The 1960 Annual Conference of the Surgeon General with the State and Territorial Mental Health Authorities was held in Washington, D. C., January 6-7.

The theme of this conference was: "The Integration of Specialized Mental Health Programs into a Total Mental Health Program." The specialized areas considered included aging, alcoholism, emotional problems of children (especially juvenile delinquency and residential treatment needs) mental health education, mental retardation and school mental health. Each of these areas was discussed in group meetings, which developed recommendations pertinent to the area under discussion. These recommendations were then submitted

to the total group at the Conference with the Surgeon General, for action.

An address, "The Manpower Crises in Mental Health," by Dr. George W.Albee, author of the Joint Commission report on this subject, pointed out the current problems in recruitment and training of mental health personnel. A report from the Ad Hoc Committee on Planning for Mental Health Facilities completed the conference agenda. This Committee is composed of representatives of the State Hospital Survey and Construction Authorities and State Mental Health Authorities.

The published report of the Proceedings and a Progress Report on recommendations resulting from this Conference have been prepared and distributed to mental health authorities and other appropriate personnel active in the development of State and national mental health programs.

The Conference recommendations were as follows:

1. Amendment of Social Security Laws

That the Secretary of Health, Education, and Welfare propose to the Congress legislation to amend existing social security laws so that they do not discriminate against persons with any type of illness, mental or physical, and in the meantime that the present wording of the portion of the Social Security Act governing public assistance benefits be interpreted so as to specify that only individuals physically residing in a mental hospital be excluded from assistance benefits.

2. Admission of Alcoholics to General Hospitals

That the general hospitals, particularly teaching hospitals, be encouraged to admit alcoholics for treatment.

3. Orientation in Alcoholism Activities

That the Public Health Service be requested to provide short courses involving personnel from several States in appropriate places throughout the country to give instruction and orientation in the development of alcoholism program activities.

4. Integration of Community Services

That, wherever appropriate, alcoholism services be incorporated with other community activity and that mental health centers, if they are not now serving alcoholics, be encouraged to do so.

5. Research Program for the Emotional Problems of Children

That the Public Health Service provide leadership in working with the States in research on emotional problems of children, particularly evaluative studies of ongoing programs, testing new techniques and follow-up studies of treated and untreated children.

6. Survey of Mental Health Information and Education Practices

That the Public Health Service conduct or support a survey of current patterns of mental health education and information programs of the various States with particular attention to program content, staff, techniques, evaluation methods and results and to publish a report which can be used as a resource manual to be made available especially to the State Mental Health Authorities.

7. Integration of Services for the Mentally Retarded with Other Medical and Related Services

That the Public Health Service encourage the development of comprehensive diagnostic and treatment services for the mentally retarded integrated with other medical and related services at the local community level.

8. Services for Mentally Retarded and Borderline Adults

That the Public Health Service investigate through sociological and epidemiological studies the needs of mentally retarded and borderline adults and the resources available for them.

9. Education and Training of Personnel in the Field of Mental Retardation

That the Department of Health, Education, and Welfare emphasize in its training and assistance programs the subject of mental retardation. This applies to the various appropriate specialities in medicine and other related professions and to nonprofessional groups serving the mentally retarded.

10. Future Considerations of Mental Retardation

That mental retardation be included as a major agendum at the 1961 Conference of the Surgeon General with State and Territorial Mental Health Authorities.

11. Distribution and Collection of Information Regarding School Mental Health Activities

That the State Mental Health Authorities be supplied with copies of the report "School Mental Health Activities of State Mental Health Authorities" and that each State Mental Health Authority be requested to provide supplementary information about its activities in the school mental health area to be included in a periodic revision of this report.

12. Joint Activity of the State Mental Health Authority and the State Department of Education in Developing School Mental Health Programs

Whenever feasible, that the State Mental Health Authorities take the initiative in establishing appropriate liaison mechanism with Departments

of Education so that they can together, in a mutual relationship, and on a joint basis, analyze and develop the comprehensive school mental health programs in the State.

13. Expansion of the Staff for School Mental Health Consultation

That the staff for school mental health consultation services of the Community Services Branch be expanded in order to provide more intensive services to the States where a need for additional services exists.

14. Expansion of Training Resources for School Mental Health Personnel

That the Public Health Service expand the programs for the training of school mental health personnel.

15. Contracting for Special Studies in School Mental Health

That the Public Health Service be encouraged to contract for special studies in school mental health programs.

Conference of the Surgeon General with the State and Territorial Health Officers

The Conference, held in San Francisco, California, October 28, 1960, made the following recommendations related to mental health:

Chronic Illness Insurance - "That the Surgeon General develop experimental programs wherever feasible which include extended insurance coverage as a basis for providing general hospital care, chronic hospital care, nursing home care or care of patients in their homes; and that the State and Territorial Health Officers give every support in their jurisdictions should such programs develop in their areas."

Medical Care Programming - "That the Public Health Service provide leadership in the medical care area by creating a program unit which will have responsibility for collecting and disseminating information, developing training for professional personnel, participating in studies and demonstrations and consulting with all groups interested in this field."

Mental Health Consultant - "That the Public Health Service make a special effort to provide at least one mental health consultant to each area office of the Division of Indian Health."

The annual meeting of the Association of State and Territorial Health Officers, held October 28, 1960 in San Francisco, California, recommended

the following which are of special interest to mental health programs:

Fragmentation of Community Health Programs - "That the Council of State Governments, in cooperation with the Association of State and Territorial Health Officers, in the interest of economy and efficiency be requested to study the problems of fragmentation of health programs when various aspects of a total state health program are considered for placement in other than health agencies of state government."

Metropolitan Health Planning - "That state health departments initiate and participate in metropolitan health planning to facilitate cooperation among health, planning, public works, and public welfare agencies in meeting the present and future needs of expanding communities; and that the Public Health Service be requested to conduct training, research, and field studies in this area."

Home Care - "That the several State and Territorial Health Departments encourage the development of comprehensive home care programs and other care of patients in the home."

Aspects of Traffic Accident Control - "That each State and Territorial Health Officer establish and maintain close and active cooperation with the State Motor Vehicle Administrator in his State on problems involving the human aspects of traffic accidents."

Medical Care of the Aged - "That in the face of existing legislation, health departments at all levels be urged to participate with relevant bodies in activities such as contracts, cooperative efforts, consultation procedures, advisory bodies, and other arrangements which will achieve maximum coordination of efforts in the development of health services to the aged."

DEVELOPMENTS IN STATE AND LOCAL PROGRAMS

Introduction

The continued popular demand for stepped up action in mental health was reflected in two major reports that received national attention. According to the President's Commission on National Goals:

> "Some 17 million persons suffer from mental illness in this country; it costs state governments over $1 billion per year. A maximum research effort, a substantial increase in the number of mental health clinics, and further progress in improving state mental hospitals are all part of the necessary effort to cope with it.
>
> " An important welfare objective is to learn more about the causes and methods of prevention of juvenile delinquency and family breakdown. There is great need for sustained study in order better to understand this complex community problem. It requires co-operative attention and action by many professions, community services and organizations."

The Platform adopted by the Democratic National Convention (1960) had the following statement:

> "Mental patients fill more than half the hospital beds in the country today. We will provide greatly increased Federal support for psychiatric research and training, and community mental health programs, to help bring back thousands of our hospitalized mentally ill to full and useful lives in the community."

Another publication which attracted popular attention was the book "Mental Health Education - A Critique." This was a report of a national meeting on mental health education held at Cornell University. This controversial report, issued by the Pennsylvania Mental Health Association, by and large deprecated the value of mental health education in the area of promotion and prevention but endorsed educational activities about mental illness.

Joint Commission on Mental Illness and Health

In the past year the following task force reports have been published:

1. "Current Concepts of Positive Mental Health"
2. "Economics of Mental Illness"
3. "Mental Health Manpower Trends"
4. "Americans View Their Mental Health"
5. "Community Resources in Mental Health"
6. "Epidemiology and Mental Illness"

These task force reports have aroused wide interest. We look forward to the publishing of the last task force report "Patterns of Patient Care."

The final report of the Joint Commission on Mental Illness and Health is in the second draft stage at the present time. To some degree it summarizes the materials in the various task force reports and tries to answer two questions, the first being "Why Has Care of the Mentally Ill Lagged?" and the second, "How Can We Catch Up?" The final report will contain definite recommendations both for program and for legislation. It is expected that it will be ready to present to Congress early in the next session.

State Organization

In four states (Alaska, Georgia, Nevada, North Carolina) the prestige and responsibilities of the community mental health program were strengthened by raising the program to Division status. In Utah the Division of Mental Health was raised to Bureau status. Puerto Rico had a different kind of change in which the Bureau of Mental Health was placed under the head of the Puerto Rico psychiatric hospital.

The Georgia Public Health Department took over the mental hospital program on January 1, 1960. Later in the year the same Department was also given responsibility for the State School for Mental Defectives, and for the alcoholism program previously carried by the State Commission on Alcoholism, which was abolished. In a similar move, in Louisiana, the Commission on Alcoholism became part of the State Department of Hospitals (the mental health authority). Although the trend in the last four years seems to be to integrate independent alcoholism agencies into older and larger State departments (such as the department of health or mental health), Nevada reversed the field by establishing an independent State alcoholism agency.

The unique New York Interdepartmental Health Resources Board, which many regarded as a possible model for other States, was abolished this year.

Instead a new Interdepartmental Health and Hospital Council was organized which is made up of the State Commissioners of Education, Health, Mental Hygiene, Social Welfare and the Superintendent of Insurance. The major change is that the Council will not operate projects. Rather it will concentrate on interdepartmental program study, planning and development.

In at least one third of the States, the organizational location of the community mental health program was a major issue. The pressures for reorganization were varied and complex; including dissatisfaction with the existing program, a power struggle and a philosophic struggle between public health and psychiatry, an attempt to bring community programs and mental hospital programs close together, and the belief that the mental health program was so large that it required independent status as a department. Whether or not such changes are desirable, top program and administrative staff in many States are expending a large part of their energies in these organizational battles.

State-Local Community Mental Health Laws

In 1960, the passage of new community mental health laws providing for State grants to localities was considered in several States, but was not enacted in any State. However, there is little question that these laws will be a live issue in many of the 1961 State legislative sessions.

Wisconsin, which passed such a law in 1959, had the typical experience of rapid expansion of services. Thirteen clinics have been approved to receive State aid and applications for 3 other clinics are pending. Of these 16 clinics, 4 are located in communities which previously did not have such a service. In the clinics that were in existence before the new law went into effect, man-hours of professional staff service have increased 45%. In the biennium 1959-61, $400,000 was budgeted for this program; in the 1961-1962 biennium, $1.1 million was budgeted.

Under its new community mental health law, Minnesota now is supporting 14 local mental health centers. A typical development stemming from these laws has been the closing down of State operated clinics. Of the four State clinics in Minnesota, two have been taken over by the local community, one was closed and the last integrated with another service. Minnesota has had exceptional success in recruiting for its professional positions in the local community programs, even those in rural areas. In terms of funds, in a 3-4 year period the State funds for grants to localities have grown from less than $100,000 a year to just over $1 million.

In California, $2.8 million in Short-Doyle funds for assistance to local mental health programs is available in fiscal 1961 - an increase of $963,000 over the previous year.

The pressure for increased funds was also felt in New York State. Here the State legislature raised the maximum of State reimbursement for community mental health programs from $1.00 per capita to $1.20 per capita.

Community Clinics

Provisional data on outpatient psychiatric clinics in 1959 shows a number of gains in terms of services available compared to 1954-55: (1) The number of clinics grew from 1,234 to 1,429, an increase of 16 percent. (2) Scheduled weekly professional man-hours of clinic service increased by 37 percent, to 258,000 hours. (3) The number of professional man-hours of clinic service available per week for each 100,000 population rose from 115 to 145. (4) Every State now has outpatient clinic services.

Significant innovations, pilot projects and demonstrations are being conducted in some of the community clinics in the country. The Northeastern South Dakota Mental Health Center (Aberdeen) is placing major emphasis on emergency treatment - very brief, supportive and medical treatment including the use of drugs. The program is unusual because services are available on call, both personally and by telephone call outside of regular office hours, and efforts are made to visit the patient when the patient can't come to the office.

With the support of a Mental Health Project Grant, the Department of Psychiatry of the University of Texas Medical Branch is experimenting with multiple impact, intensive brief psychotherapy for severely disturbed adolescents who would ordinarily require long-term intensive treatment. The program involves interviewing and treatment of the adolescent and his family for a two-day period.

In 1960, the Mercer Area (N. J.) Mental Hygiene Clinic became the N. J. Mental Health Center - a Training and Demonstration Clinic. It is expected that the clinic will become a model for community clinics. Its main focus is on demonstration methods and procedures which can be effective in meeting the needs of preventive community mental health.

Minnesota is using Federal grant-in-aid funds to experiment with adding the following kinds of staff to the traditional disciplines in different clinics: (a) speech therapist (b) social scientist (c) child group worker (d) marital counselor (e) psychiatric nurse (f) public health nurse. Also, in one community in Minnesota, staff of the mental health clinic and of the State hospital have cross-appointments as staff of the other facility. Both staffs are collaborating on community consultation and education.

In a variation of Florida's "mental health worker", North Carolina is moving to establish psychiatric social worker positions in health departments surrounding those areas which now have mental health centers. These

workers will be supervised one day per week at the nearest mental health center. The other four days will be spent in screening patients in their own counties for referral to the nearest clinic, in doing limited therapy under the direction of the clinical psychiatrist and in providing consultation to other community workers.

A report for 1958 issued by the Biometrics Branch, National Institute of Mental Health indicated that in 595 outpatient psychiatric clinics, 94% of the scheduled staff hours were spent in direct services to patients, that is primarily diagnosis and treatment. Only 6% of the man-hours were devoted to community oriented services such as mental health education, consultation with other agencies, participation in community planning and coordination activities.

Aging

The White House Conference on Aging (to be held in January 1961) has led to widespread community interest and concern about problems of the aged.

For many years mental hospitals have struggled with the problem of the aged. Screening devices have been established to prevent aged who are not seriously disturbed from entering the mental hospital and attempts have been made to discharge aged patients already in the hospital. Nursing homes have been widely considered to be the solution to the problem. However it was no surprise when the Senate Subcommittee on Problems of the Aged and Aging issued a 1960 report of a survey of nursing homes. The report found: (1) "a shortage of 127,024 beds" (2) "Fifty percent of the existing 307,681 nursing homes are unacceptable - under the standards of the Hill - Burton Act" (3) "personnel often is inadequately trained and frequently there is no provision for medical care....." (4) "the vast majority of nursing homes provide no rehabilitation or restorative services." Attention to nursing homes has been one of the ways that State mental health authorities have begun to take action in the field of aging (e.g. Missouri, Minnesota, South Dakota, Nebraska).

Specialized community mental health services for the aged continue to be scarce. An outstanding project is Senior Citizens, Inc., a community center for elderly people in Nashville, Tennessee, which combines a program of services, training and research. An increasing number of the aged served by this Center are homebound and are being provided with medical care, social services and instruction in self-maintenance.

Federal grant-in-aid funds are being used in Oklahoma for a survey of needs and resources for the aging. This project, conducted in cooperation with the Department of Preventive Medicine, Oklahoma Medical Center, is part of a plan to develop an information center and institute on gerontology at the Medical Center. Federal grant-in-aid funds are also being used in Missouri for a study of the care of the aged in the rural areas of the State.

Alcoholism

Interest and activity in alcoholism programs continued at a high level. More public health and mental health staff are becoming involved in serving alcoholics.

In the fast spreading programs of follow-up and after-care for patients who have been hospitalized, public health nurses and social workers are working with alcoholics as well as other types of patients. The Health Departments in Massachusetts and Washington are attempting to develop a comprehensive inpatient and outpatient service for tubercular alcoholics.

In the other direction, alcoholism program staff are trying to develop closer relationships with staff in public health, welfare, vocational rehabilitation and education. The independent alcoholism commissions in Arkansas, Colorado, North Dakota and Utah have made special efforts to work more closely with State health departments.

New specialized facilities for alcoholism are being established. The Washington Department of Health granted state aid to set up two new alcoholism information and treatment centers in Vancouver and Tacoma.

The Louisiana Legislature appropriated about $150,000 for additional and separate units for inpatient treatment of alcoholics in State general hospitals and mental hospitals. Included also were funds for an outpatient center for alcoholics in New Orleans.

Like many State community mental health agencies, some of the State alcoholism programs make grants-in-aid to other agencies. For example, the Division of Alcoholism of the Illinois Department of Public Welfare made grants-in-aid totalling $125,000 to seven non-state agencies in fiscal year 1961. In addition, the Division of Alcoholism itself operated two demonstrations, the new inpatient pilot project at Peoria State Hospital and the outpatient Warren Clinic in Chicago. Both of these projects are testing the effectiveness of the psychiatric approach in treatment and rehabilitation of alcoholics.

Another important development has been the increasing availability of general hospitals for the care of alcoholics. A study sponsored by the California Department of Public Health and the American Medical Association at Mt. Zion Hospital in San Francisco revealed that acute alcoholics can be successfully treated in a general hospital without segregation, without restraint, with no more trouble than other acutely ill patients. During this project 62 patients were admitted a few at a time for periods up to a week or more. They were treated only for the worst part of their acute alcoholism episode. For help with their deep-seated emotional problems, they were referred after discharge to psychiatrists, an alcoholic clinic or Alcoholics Anonymous.

A Massachusetts General Hospital project (Title V) in Boston is concerned with "alcoholism treatment and initial therapeutic contact." Preliminary findings indicate that those alcoholic admissions who received care and attention from well-prepared personnel upon arrival at the emergency ward are much more likely to enter into and continue treatment for their alcoholism problem than are similar admissions who do not receive such initial attention and care. Referrals were made to a variety of social agencies and it was found that some agencies did not want to work with the alcoholic. Other Title V projects include a just completed project in Nebraska to prepare and assist general practitioners in providing services to alcoholics and an evaluation in Florida of clinic services provided to a group of alcoholics who have been in correctional institutions.

Among the special alcoholism activities supported by Federal grant-in-aid funds are an Alcoholic Information Center in Wyoming, the Willmar (Minnesota) Follow-Up Service, a Survey of Community Attitudes and Resources in the area of alcoholism in St. Louis, Missouri and a study of alcoholism and traffic offenders in Kansas.

Drug Addiction

Special mental health services for drug addicts continue to be scarce. Three States (Georgia, Maryland, New York) passed legislation providing for the commitment or treatment of addicts in State mental hospitals. In New York, an appropriation of $300,000 was designated for the development of special State hospital facilities for the care, treatment and rehabilitation of addicts. Two new units for the care, treatment and rehabilitation of narcotic addicts will be established at Central Islip State Hospital and the Utica State Hospital.

The New York State Division of Parole issued a report evaluating their three year "Special Narcotics Projects" which began in 1956. In this experimental project, four well-trained caseworkers tested the efficacy of intensive, "authoritative" case-work with a small group of young drug addicts on parole. In the last year of the demonstration, group therapy sessions were conducted by a psychologist. Although the evidence was not conclusive, there were many indications of the success of the service and the Governor has recommended that the project become a permanent part of the operations of the Division of Parole.

A similar experimental program on a larger scale is under way in California. As part of a treatment and research program for narcotic prisoners at the California Institution for Men at Chino, near Los Angeles, a parole system has been established for addicts in which a condition of parole may be participation in the experimental program. In this program, parole agents carry a caseload of 30 former prisoners. In addition to individual counseling, each parole agent does group counseling, mostly

in the evening hours. The project is also testing the effectiveness of drugs like nalline for the detection, control and treatment of addiction. If an addict is found to be taking drugs, he may be returned to prison.

The original appropriation for this project was $125,000 in 1958. In 1960, the California Legislature raised the appropriation to $500,000 which will make possible the opening of similar service units in other parts of the State.

Mental Retardation

New community programs for the mentally retarded continue to be established. Increasingly mental health personnel are accepting mental retardation as an essential part of a comprehensive mental health program.

Day care centers for the mentally retarded are spreading. Delaware's day care centers serve mentally retarded children when they have an I.Q. below 35 - a group usually considered to require institutional care.

The Louisiana legislature appropriated $200,000 to the Department of Hospitals (the State Mental Health Authority) to provide services to the retarded in guidance centers or clinics and to establish day care centers.

To cope with the increasing number of mentally retarded children awaiting admission to the State institution, the Michigan Department of Social Welfare plans to locate social workers in selected areas to provide services to the mentally retarded in the community. Emphasis will be placed on: (a) better screening for institutional care (b) immediate attention to diagnosis and a treatment plan for those on the waiting list (c) more intensive work with vocational rehabilitation staff.

The Pennsylvania Department of Welfare has been allocated $240,000 to help communities establish sheltered workshops for the mentally retarded. These workshops expect to demonstrate how the mentally retarded, formerly believed to be in need of institutional care, can live normal, productive lives in the community.

An unusual program initiated in New York State attempts to prevent mental deficiency due to phenylketonuria. The Department of Mental Hygiene will provide a special diet formula for recognized cases in the community. A very small number of children in the State have this type of disorder. The Michigan Health Department also is developing plans for casefinding of children with phenylketonuria by following up siblings of patients with phenylketonuria in state hospitals and school classrooms for mentally retarded children.

The New York Department of Hygiene released a significant report of a study on factors in the institutionalization of the mentally retarded in New York City. Since it was believed that persons with an I.Q. of less than 20 are generally committed soon after diagnosis, this group was omitted from the study. Of the remaining mentally retarded, it was found that about 1 out of every nine with an I.Q. 20-49 is institutionalized and only one out of about 100 mentally retarded with an I.Q. of above 50 is institutionalized.

Behavior problems outside the home was an important factor leading to institutionalization. Sexual offenses almost invariably resulted in placement in an institution. On the other hand, adjustment problems in the home without accompanying trouble in community was a factor in commitment mainly among the low grade retarded from middle class homes.

Broken homes was another important factor influencing the rate of institutionalization. More than nine out of ten of the re- rded living in the community resided with both their natural parents while this was true for only 4 out of ten of those placed in institutions.

As compared with mentally retarded living in the community, it was found that institutionalized mentally retarded often came from homes known to the welfare department, had appeared before the courts for charges of neglect and were living in slum areas. Parental inadequacy was found to play a significant role in the decision to institutionalize a child while the parents' love or affection for the child seemed to be a minor factor.

School Mental Health

Based on consultation requests received, the current mental health related interests of public school educators are on: (a) the use and patterns of supervision of school psychologists and school social workers; (b) the development of programs of screening and the educational rehabilitation of emotionally handicapped children; and (c) the management of anxiety and behavior problems in the instructional programs. There is also considerable interest in (1) administrative leadership and staff morale; (2) learning process, especially in the gifted child; (3) learning machines; and (4) the use and misuse of testing instruments. The education literature continues to reflect a concern with individual differences, especially in reference to problems of tailoring education programs to meet the needs and motivations of children in lower class culture. The writings, research applications, and consultation requests received show a growing interest in the contribution of the social sciences.

The continued activity of school systems in employing large numbers of mental health trained personnel necessitates much greater attention by State Mental Health Authorities to this area of programming so that two overlapping mental health programs do not emerge in local settings.

State Mental Health Authorities in Kentucky, Tennessee, Georgia, Pennsylvania, New Hampshire, Kansas, North Dakota, Minnesota, California, New Mexico, and Arkansas took new steps this year to work more closely with their respective State Departments of Education and colleges on such projects as classes and services to emotionally disabled children, guidance services, alcohol education, and the training of teachers in mental health.

The Kentucky Department of Mental Health has worked to set up a staff of school mental health consultants as part of the State Department. Kentucky plans to place these school consultants in regions throughout the State. During 1960, two additional full-time counselors were added. Consultation was provided to school principals and faculty; direct services to individual children was not provided.

Alabama's new pilot project on the mental health of the school age child may prove to have significance for the field. The Division of Mental Health, State Department of Public Health has begun a school project in Bullock, Crenshaw and Etowah Counties which is focused on developing methods and techniques for identifying and correcting mental health problems at an early age through intervention in the school. In these three counties, all children entering the first grade are screened for mental health problems then psychological tests and findings for each child are discussed with parents and teachers. If a child has difficulties in school, efforts will be made first to resolve the difficulty within the school. If these efforts are not successful, the school may call the public health nurse to work with parents and teachers to help the child. For children who need still further help, assistance will be available to the teacher from consultants of the Division of Mental Hygiene and some children may be referred to a mental health clinic.

Psychiatric Emergencies

Although the notion of providing psychiatric emergency care and treatment in the home and community is exciting and intriguing, only a few places in the country are experimenting with this kind of service. At the Boston State Hospital, (Title V Project), intensive psychiatric evaluation is provided in the home at the time when a psychiatric emergency occurs. A psychiatric team made up of a psychiatrist, social worker and nurse visits the family when such an emergency occurs and works intensively with the family as individuals and as a group. Diagnosis and treatment are provided by the clinical team in cases where it is felt that the patient can remain outside the hospital. Preliminary findings from an assessment of this three-year project indicate that the emergency service is able to treat in the community 40% of cases that would have been destined for the mental hospital under ordinary conditions.

The Florida Health Department is planning a demonstration in Pensacola where three psychiatrists will be employed to provide consultation on psychiatric crises. The consultation is to be provided to general practitioners

by the psychiatrist either in person or through the use of telephone.

References to psychiatric emergency services are also found in the sections of this report entitled "Community Clinics" and "Mental Hospitals."

General Hospitals

In recent years there has been a remarkable increase in psychiatric units in general hospitals. A recent survey of psychiatric patients in general hospitals (issued by the Joint Information Service of the American Psychiatric Association and the National Association for Mental Health) revealed that in 1958 the number of psychiatric admissions to general hospitals was larger than the admissions to State mental hospitals. Between 1954 and 1958 the number of general hospitals in the United States accepting psychiatric patients increased by forty percent - from 563 to 789. Of all general hospitals, 19% accepted psychiatric patients in 1958 as compared with 12 percent in 1954. Psychiatric units are most common in the large general hospitals in cities. Of the general hospitals with over 500 beds, 90% reported that they admit psychiatric patients.

Illustrative of the public interest in psychiatric facilities in general hospitals is the recent state-wide referendum in Alabama, which approved a $3 million bond issue for the construction of a 100 bed psychiatric hospital unit as part of the University of Alabama Medical Center. The measure passed by a vote of eleven to one, the biggest favorable majority in the history of bond issues in Alabama.

Georgia's "Intensive Treatment Program" was expanded to include the Grady Memorial Hospital which opened a psychiatric unit in conjunction with the Emory University School of Medicine. The "Intensive Treatment Program" treats in general hospitals many patients who would ordinarily have been committed to the State hospital.

As an example of a general hospital which provides an unusually comprehensive program, the Montefiore Hospital, New York City, opened its psychiatric unit in 1960. The program includes: a) inpatient services b) day care c) night care d) outpatient clinical services e) home care, including visits by resident psychiatrists to the homes of patients or their families.

Connecticut, which has an extensive program of State aid to psychiatric units in general hospitals, is using Federal grant-in-aid funds for a study and evaluation of these inpatient resources.

Day and Night Hospital Care

Only a short time ago, the concept of day hospital care and night hospital care was relatively unknown. The recent survey of general hospitals by the Joint Information Service found that there were 76 general hospitals in the United States which had day programs for psychiatric patients that did not remain in the hospital overnight. Fifty-three of the United States hospitals had night care programs for patients who were not in the hospital during the day. Altogether close to one-tenth of the United States hospitals surveyed had either a day care or night care program.

The California Legislature appropriated $150,000 to the Department of Mental Hygiene to open a new day treatment center in San Diego, the first of its kind in the State.

Besides general hospitals, day or night care is often a part of the program of a State mental hospital. For example, Metropolitan Hospital in California inaugurated a day care program this year. The new Dammash State Hospital being organized near Salem, Oregon is to have 400 inpatient beds, a day hospital and outpatient service.

A recent survey of the American Psychiatric Association members showed that the idea of day treatment was rated higher than 39 other types of treatment. Day care was seen as having the following values:

> Some family life is retained by the patient who returns home at night.
>
> Supervised socialization, work and play are better developed in this setting.
>
> There is not the prejudice which attaches to the usual state hospital commitment.
>
> The family physician is more easily involved in the patient's treatment.
>
> There is greater possibility for volunteer help from the community.

Commitment Laws

The commitment provisions of the English Mental Health Act of 1959 will undoubtedly have far-reaching effects on United States commitment laws and practices. The English law no longer requires court action for compulsory admission or detention in a mental hospital. Instead two medical opinions are required, one of which must be given by an expert. The changes

in the new Act are designed to enable patients with a mental disorder to be treated like persons with a physical ailment. Patients are encouraged to seek treatment promptly and voluntarily. Assessment of a patient's mental condition is considered as a medical judgment rather than a legal matter.

As a step in the same direction, the New York Legislature enacted a law which provides for admission to a mental hospital on the certificate of two physicians and a petition by a relative. At least one of the physicians must be a psychiatrist. Prior to the expiration of 60 days, the patient's status must be changed to that of a voluntary patient, or to that of a non-voluntary certified case. Patients admitted under the new procedure cannot be detained without a court hearing on this admission for more than 10 days or for more than 5 days after giving notice of desire to leave whichever is longer, if there is any objection by the patient or by any person acting on his behalf.

In many of the mental hospitals in the United States increasing emphasis is being placed on voluntary admissions. For example, the (Ind.) Evansville State Hospital reports that only 4% of its admissions used court commitment proceedings. Under a 1957 law, patients come in for a maximum ninety-day observation period and they generally sign voluntary admission papers within thirty days after entering the hospital.

Mental Hospitals

Exciting changes are taking place in many of the nation's mental hospitals. Kentucky is developing an "open door" plan in all four of its State mental hospitals. The Pilgrim State Hospital (New York), a 14,000 bed hospital, has been divided into 2000 - 3000 bed units in an effort to achieve the advantages of a small hospital within the framework of a large hospital.

At the Hudson River State Hospital (New York), a pilot community-hospital project will provide comprehensive treatment service (inpatient and outpatient) for the mentally ill in a selected community (Dutchess County). The objective is to determine to what extent hospitalization can be reduced by such a service, what kinds of patients require hospitalization and which can be treated in a community facility without hospitalization. Within the large hospital, a "subhospital" closely linked with the day hospital service, has been established. The next stage of development calls for a "pre-care" service, that is, psychiatric emergency service to provide consultation and treatment before a decision is made whether or not to hospitalize.

In a related development at the Clarinda Mental Health Institute (Iowa), the hospital has been reorganized into units of care focused on the county geographical boundaries. The patient is admitted directly to a unit which services the county rather than to a functional system in terms of an

acute ward or a chronic ward. The psychiatric team, which cared for the patient in the hospital, follows the patient into the community to help him plan for his convalescence whether in his own home, in a foster home or a nursing home.

Formal administrative mechanisms to encourage closer hospital-community relationships are being developed. New York State has been divided into 10 mental health regions and regional advisory committees set up to bring about better coordination of the state hospitals and community mental health services.

The State Health Department and State Department of Mental Hygiene in Maryland agreed to a coordinated mental health program in which local health departments will take responsibility for providing services in the community during the stages of pre-admission, admission to the State hospital, inpatient stage, return to the community and followup.

Inpatient and Day Center Care for Emotionally Disturbed Children

Several State legislatures appropriated funds in 1960 for the construction of residential facilities for emotionally disturbed children. The Florida Legislature approved a plan to provide $1 million to construct a children's resident treatment center on the grounds of the South Florida State Hospital in Hollywood. Construction is to be completed in 1962.

As part of the program of the Virginia Department of Mental Health, a children's center is under construction adjacent to the Medical College of Virginia in Richmond. The Tennessee Department of Mental Health is cooperating with the Vanderbilt Medical School in establishing a Children's Psychiatric Unit, which will be used in conjunction with the training programs for the mental health professions at Vanderbilt University, Peabody, and the University of Tennessee. Pennsylvania and Washington are also establishing residential centers for children.

The Dayton (Ohio) Children's Psychiatric Hospital has completed its first year of operation in its new building. This "Children's Center" is designed to serve as a comprehensive treatment residence for emotionally ill children. Three types of services are being offered: (a) residential services (b) day-hospital services (3) outpatient clinic. The Hospital is also used for professional training and research.

Paralleling the interest in day hospitals for adults, experimentation is underway with day treatment centers for seriously disturbed children. In Tennessee, a mental health clinic is experimenting with a day care school for a small number of psychotic children. Federal grant-in-aid funds are being used to help support two day treatment centers for emotionally disturbed children in New York and a day care program for autistic children at the Bridgeport (Connecticut) Rehabilitation Center.

Aftercare and Rehabilitation

Aftercare services for ex-mental hospital patients are fast becoming an accepted part of most State mental health programs. Louisiana has organized five after-care centers - two use the facilities of guidance centers (clinics) and three are attached to State hospitals. The services of these centers include drug therapy, social casework, psychotherapy and group therapy, consultation with patient, family members and community agencies and referral to community resources.

In Illinois, local community clinics receiving State grants are replacing the outpatient clinics of the State hospitals in providing aftercare services.

Public health nurses in local health departments in Alabama have primary responsibility for aftercare. Nearly half of the State's 67 counties now have such services. In many Alabama counties the local mental health association is participating in these services by provision of drugs.

A similar program involving public health nurses in North Carolina was first begun in 1954 and now has been expanded to 19 counties, largely as a result of pressures from the counties that wanted to participate. In this service, in addition to aftercare, the public health nurses work with the families of patients at the time of admission to the hospital.

An informal review of North Carolina's experience reveals that the nurses feel satisfied that they are needed as almost invariably the patient's family is distressed and baffled in the first few weeks after the patient is admitted to a State hospital. About 1/3 of the families have other types of public health problems. Private physicians, primarily general practitioners, are pleased about referrals to them and are glad to receive information about their patients from the public health nurses. Close contact between the local health department and the State hospitals is seen as an urgent and continuous need. Problems in paying for drugs and drug dosage are still largely unresolved.

In Michigan, social workers are being assigned to localities to develop and provide aftercare services, with supervision provided by the State hospital. At the same time, several local health departments are trying out a followup service using public health nurses. The Detroit Consultation Center, supported by Federal grant-in-aid funds, is primarily an after-care service but is to be developed into a pre-admission service also.

The Iowa State hospitals, also, are developing outpatient services for the mentally ill and placing social workers in communities to provide aftercare.

The California program of placing mental patients in foster family homes has grown so large that the State legislature this year appropriated

funds for a new unit of 13 social workers which will specialize in finding foster homes for patients discharged from the State hospitals.

Marked gains have been made in increasing vocational rehabilitation services for the mentally ill and mentally retarded. The number of mentally ill persons prepared for and placed in successful employment through the Federal-State program of vocational rehabilitation increased from 1793 in 1955 to 4000 in 1960, a rise of 123 percent. The percentage gain for the mentally retarded was even larger - 314%. The increases for these two categories were larger than for any other disability.

Federal grant-in-aid funds are helping to support the Cleveland, Ohio, Half-way Center. Day and evening services are provided to help patients discharged from the mental hospitals to readjust to the community. Particular emphasis has been placed on work with vocational rehabilitation agencies.

Manpower and Training

The shortage of professional manpower continues to be a major bottleneck in almost every part of the country.

This year the National Association of Mental Health launched a "Mental Health Careers" program. The Careers program includes the following: (1) Giving information to teenagers and attempting to interest them in job opportunities in the mental health field (2) Providing background information on the mental health field to guidance workers, vocational advisors, principals and teachers (3) Developing cooperative recruitment activities with mental health professional organizations (4) Forming youth volunteer groups to take young people into hospitals on a volunteer basis so they may get first hand knowledge of mental health practice.

The response to an opportunity for work and study in the field of mental health, sponsored by the Western Interstate Commission on Higher Education, suggests that this is a promising method to inform young people about the mental health field. Twice as many young people as could be accepted applied for work as "mental health internes" during a 10 week period in the summer of 1960. Two pilot programs, each involving 40 students, were developed in cooperation with the University of Washington, the University of Colorado and the departments of institutions in the two States.

Also in the summer 1960, New Jersey began a pilot program of training for senior medical students. Students were exposed during the summer months to various roles in a mental hospital setting.

Many of the individual State programs were making significant efforts to deal with the manpower problem through stipend programs. A referendum was approved in Georgia authorizing the development of a research and training program using funds which are collected for the support, care and treatment of mental patients.

In fiscal year 1961, Ohio has budgeted $1.9 million for accredited training of mental health personnel. The following number of traineeships are budgeted: 90 psychiatric residents, 80 social workers, 22 nurses, 45 psychologists, 25 activity therapists and 3 pharmacists. In addition the State has an extensive program of non-accredited inservice training.

Similarly Louisiana expects to spend $600,000 to provide stipends for 22 psychiatrists, 4 neurologists, 20 psychologists, 26 social workers and 6 nurses.

The California Department of Mental Hygiene has provided 6 staff positions at Langley Porter Neuropsychiatric Institute for a training program in community mental health.

In Maryland a new program has been initiated to place psychiatric residents in community mental health clinics in various parts of the State. The purpose of the training programs is two-fold: to provide psychiatric service to understaffed areas and to incorporate the aspects of public health psychiatry into the psychiatric residency program. The psychiatric residents have been working closely with county health department staff and have emphasized consultation and other community mental health approaches rather than treatment of individual cases.

Eastern State Hospital (Washington) launched a special two-year internship program in the field of mental health administration. The program will offer internships to psychiatrists, psychologists, psychiatric nurses, and related professional staff who hold administrative jobs in mental hospitals or clinics.

In August, 1960, the California Department of Mental Hygiene inaugurated a new type of training program for psychiatric technicians (aides). The psychiatric technicians enter a two-year accredited nursing program at a nearby junior college in order to become qualified as registered nurses. During the period that they are enrolled at the college they also continue to work at the hospital.

An unusually successful project (Title V) has been the Inservice Exchange Training Program conducted by the Southern Regional Education Board. This program has enabled mental hospital and training school employees in 13 Southern States to visit, for the purpose of securing additional training, other insitutions in the United States or Canada for a period of time not to exceed 4 weeks. This device has permitted psychiatrists, psychologists, social workers, nurses, physicians, and other mental hospital personnel to observe new techniques of hospital administration and patient care at first hand and to bring back to their own institutions the benefit of these observations. About 300 persons received grants averaging $221 each. Employees from 39 of the 50 State mental hospitals in the Southern Region and 17 of the 24 schools for the mentally retarded received grants.

Research

In 1960, the Southern Regional Education Board issued its report "Mental Health Research in the South on the Threshold of the 60's." An estimated $4.3 million was spent for research in mental health in 16 Southern States. Fifty-four percent of the funds came from the Federal government, 22% from State governments, 16% from foundations and the remaining 8% came largely from private academic institutions. Most of the research funds went to universities; about 1/5 went to departments of State government.

More than 50% of the mental health researchers included in the Survey were psychologists and about 25% were physicians (largely psychiatrists). The remainder were in a variety of professional fields including social work, sociology and nursing.

Slightly less than 50% of the respondents stated the lack of time for research was a major obstacle. Lack of funds for research was in second place (28%) and lack of professional and technical personnel was listed third (21%). Very real concern was expressed about lack of tenure for researchers.

The study found a desire among researchers for more short-term courses, seminars and in-service training opportunities in the field of research design, methodology and statistics. The requests came particularly from administrators in clinical or community agencies.

The researchers ranked the following needed services in highest priority: (1) information about sources of financial support (2) information about current research (3) information about consultants.

The mental health programs in the large, urban States continue to expand their research activities. For the 1959-61 biennium, Ohio has $2 million of State funds available for research. The Mental Health Research Institute being established at Ann Arbor, Michigan is nearing completion. The New York legislature created a Mental Health Research Council made up of the Commissioner of Mental Hygiene, 2 representatives of the legislature and 6 scientists.

The expansion of research in the California Department of Mental Hygiene is especially noteworthy. The California legislature increased research funds of the Department of Mental Hygiene from $200,000 to a total of just over $1 million in 1960. At the end of the year the Neuropsychiatric Institute at the University of California at Los Angeles was scheduled to open. This Institute will be operated as part of the University's School of Medicine, under Department of Mental Hygiene administration. Also, plans are moving ahead for a new million dollar research building at Pacific State Hospital, the first such unit at any of California's State hospitals.

A set-back to mental health research was the decision of Yale University to discontinue the Yale Center of Alcohol Studies and the Laboratory of Applied Bio-dynamics. However, current studies will be supported until completion and the summer school training sessions will be held as planned in the summer of 1961.

Needs and Problems

In the annual reports of the regional mental health consultants, the following needs and problems in State programs were frequently mentioned:

1. Shortages of professional mental health staff, especially psychiatrists.

2. Staff turnover in the top administrative positions.

3. Low salaries.

4. Organizational battles, especially about establishing a separate State mental health agency at cabinet level.

5. Extending the geographical coverage of services.

6. Developing promotional and preventive community services, beyond diagnosis and treatment.

7. Developing mental health services in social problem areas e.g., aging, alcoholism, juvenile delinquency, mental retardation, etc.

8. Expansion of psychiatric services in general hospitals.

9. Strengthening and utilizing the services of general practitioners.

10. Closer integration of community mental health with public health programs.

11. Closer relationships between training, research and service programs.

12. Expansion of training and research activities.

13. Long range planning for the development of a comprehensive, coordinated State mental health program.

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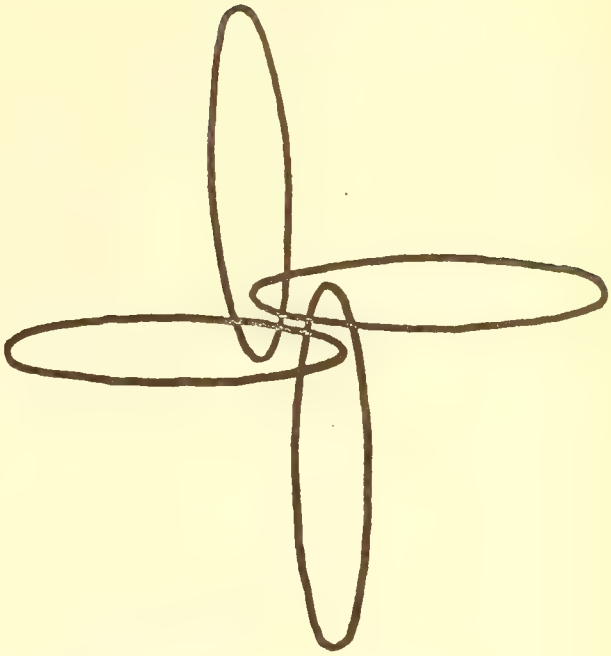

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ANNUAL REPORT

Thirteenth Year in Prince George's County

MENTAL HEALTH STUDY CENTER
1000 Lebanon Street
Langley Park
Silver Spring, Maryland

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Public Health Service

National Institutes of Health

National Institute of Mental Health

FOREWORD

It is our desire that this annual report of the Mental Health Study Center reflect the essence of the unit. With this in mind, we have prepared a report authored by several staff members presenting at times diverse but related points of view in describing the different areas of our activities. We believe this will convey the substance of our program - the operation of multiple activities in a local community setting by representatives of several mental health disciplines directing themselves toward clinical service, consultation, research, and training.

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I. THE SETTING

"VIOLENCE IN LITTLE ROCK!" "NEW ORLEANS JEERS FEDERAL INJUNCTION!" "LOUISIANA RESTRICTS ADC!"

These events of the day compel the historian to record for posterity the struggles being waged over federal philosophy and local feelings. Newsmen will report factually the daily occurrences until a resolution of the difficulties inevitably removes the story from front page coverage. The history of relationships preceding the eye catching headlines may never appear. The real issues may remain unresolved. The techniques employed to develop a sound working relationship may be lost in the potpourri of emotions, law, politics and economics.

In view of current resistance in some sections of the Country to federal programs of education and welfare, the story of one federal health unit operating in a local setting may be particularly pertinent.

Within the framework of this demonstration in mental health, obvious federal characteristics appear in financing, administrative responsibility, and personnel selection. Development of program represents a blending of public health philosophy, community organization techniques, and sincere interest in community mental health. Acceptance of program requires local autonomy, shared concern for service needs, and joint participation in problem solving. The resume of this pilot plant's life span to date could be succinctly depicted as twelve years of uninterrupted integration into local mental health relevant activities and services. Alas! Absent from such a summary would be the energizing role of the Center itself as an integrating force in the community rendering sustenance to the relationships which it carefully cultivated.

Unknown County Becomes Showcase

Prince George's County, located in Southern Maryland, was virtually unknown to mental health personnel until the establishment of the federally financed and staffed demonstration clinic.

Its comparative anonymity in part derived from the attention given its contiguous neighbors, the illustrious seat of the Nation's Capitol, and the socially and economically renowned Montgomery County. This condition changed almost overnight. The County became nationally known as the locale for mental health demonstration activities and received widespread publicity in professional and popular journals. Even with the Center's gradual shift in emphasis toward an exploratory and evaluative function in community mental health activities, the County continued to welcome visitors from all parts of the world.

What could the visitor expect to see in Prince George's County? In the formative years of the Study Center, the visitor would observe apartment buildings, new housing, school construction projects, and shopping centers arising in every section of the County's 487 square miles. If he drove the 43 miles from north to south, he would note the growing urbanization and reflect upon the 115 percent increase in population between 1940 and 1950; on the same trip the visitor would encounter tenant farmers and gaze upon apparently endless fields of tobacco. The observer would mark the inadequacy of public health, education, juvenile, and social agency resources in the face of increasing needs and witness the County's struggle to establish services in keeping with current professional standards. Particular thought would be given to the agricultural origins of the County, its resentment of growth and newness, and the historical concentration of legislative power in the traditionally conservative and geographically isolated southern portion of the County. What is the role of the federal mental health team in such a setting?

The visitor returning to this same setting today would perceive the County's concern with the needs of a continually increasing population currently numbering 357,000 residents. He would find a renaissance taking place in those basic services essential to the community's health, welfare and education. New energetic leadership in the health department has seen this agency increasing staff daily and developing a variety of public health programs, including a rapidly expanding mental health clinic. The reorganization of the local family agency stimulated by the hiring of a well experienced, creative director, has resulted in new techniques and counselling services for families. The County's general hospital opened a new psychiatric ward this year as further testimony to the development of progressive services within the County. The school system has implemented its

programs to meet the educational needs of children whose handicaps interfere with satisfactory adjustment or achievement by the employment of psychologists, pupil personnel workers, and special teachers. Nearly all of the other County agencies have shown a similar type of qualitative program improvement.

The metropolitan concept of planning became a reality approximately three years ago with the creation of the Health and Welfare Council of the National Capital Area. This instrument was devised by citizen leaders to plan for better health, welfare and recreation services for the people of the metropolitan area. While the County retains its own planning function, there is necessary interest and involvement in the larger geographic metropolitan area. The complex makeup of this metropolitan area including various political subdivisions of Maryland, Virginia, and the District of Columbia would, indeed, prove intriguing to visiting personnel. Equally perplexing to the newcomer is the location in the County of District of Columbia foster homes and institutions. In similar fashion, the utilization of some District agencies by County residents increases the difficulties of restricting certain studies to the confines of Prince George's County. Our visitor might well inquire about the federal unit's role in this present setting.

Program and People

The developing pattern of community mental health practice by the federal team in Prince George's County has benefited from several influences. Noteworthy contributions to the execution of this practice have come from public health, community organization, epidemiology, social psychology, sociology, etc., in addition to the fundamental contributions from the professions represented on the mental health staff.

The acceptance by the community itself of the federal community mental health project is a tale of people and of peer relationships. The County is not the tolerant host to the powerful federal intruder, but rather is an active ally and collaborating colleague. Such a relationship is continually fostered by the Center's Advisory Board, a group of twelve representatives from various organizations in the County. This Board, composed of allied professionals and citizen leaders, has a long history of helping to cement the close relationship existing between the Center and the County. This vital group helps

to communicate the Center's interest in the problems affecting the County and promotes the Center's willingness to become involved in the amelioration of those problems.

The Center's sincere interest and willingness to become involved with the County's allied professionals in mutually attacking the community mental health problem is manifest through clinical service, consultation, participation in community planning groups, and education. Programs are people, and it is only through relationships with people that mutual trust and confidence result. Thus, it has been in Prince George's County, Maryland, and thus it will continue to be.

Program Goals

Historically, the goals of the unit have been to operate and to evaluate an adaptable mental health clinic aware of its own history and changing role in the community, to participate with sensitivity in an expanding county mental health program, and increasingly to engage in research studies of mental health problems ranging from the evaluation of a clinic's functions to epidemiological studies of reading disability. Within this frame of reference, the primary goal of the Mental Health Study Center has been to provide a means for studying in a local setting problems of mental health which confront those concerned with the planning and operation of mental health programs at local, state, and federal levels. From this standpoint, a functioning mental health unit and a mental health "listening post" has been in operation in Prince George's County for over twelve years in a continually changing setting.

It is interesting to note that there is little discrepancy between the goals of the unit as presently conceived compared to those outlined by the initiators of the program. Real differences are apparent, however, if one compares programs past and present from the standpoint of the expanding County itself with its increasingly complex network of mental health services and the Center's gradual transition from emphasis upon providing specific clinical services to emphasis inherent in evaluation and research.

At present we are a relatively old agency by mental health standards but fresh and vigorous in terms of our points of view. It is our point of view to recognize that we are committed to long-range goals which have been relatively unchanging but to recognize also that consistent achieving of these goals is

difficult. We recognize the problems inherent in multi-discipline team methods compounded by changing commitments to several diverse mental health activities. We see ourselves participating in social change within the County and striving for clarity in the face of ambiguous demands. Granted the mixed blessings of time, funds, and well-trained professional staff, we are endeavoring not to lose touch with our fellow professionals who are more directly on the firing line in mental health programs.

II. PROGRAM ACTIVITIES

The nature of a program is best understood by its activities. Generally speaking, the past year's activities may be described in four ways.

1. Direct patient services. Prince George's County residents were seen for evaluation, and where indicated, for treatment; services were both individual and group oriented.

2. Consultation. Advisory and collaborative services were given to various agencies both within and without the County. These covered a wide spectrum from the typical case or individual problem-centered consultation, to understanding the multi-problem family, to consultations regarding programs and intra-agency relationships.

3. Research and evaluation. Systematic exploration of problems has been confined to relatively few activities. Small projects have been concerned with the clinical service. Larger effort has been directed to the study of reading ability in the County.

4. Training. Dissemination of information and provision of practical experience in community mental health represent another major area of interest. Activities have included mental health education with County groups, a training collaboration of mental health counselors with Adult Psychiatry Branch, and training two COSTEP students in community mental health research.

CLINICAL ACTIVITIES

An Intake Policy in Operation

At the beginning, the Study Center accepted self referrals as well as those professionally referred. For the past 9 years, however, cases have been accepted only by professional referral. This resulted from the awareness that community resources should be involved with the community's mental health problems. This policy has been discussed in considerable detail by Rooney and Miller (Mental Hygiene, July, 1955).

Initial contacts with the Study Center are usually telephone requests from allied professionals for consideration of a case. In the so-called telephone consultations, the desire is to plan appropriately for the patient with the referring person. "Referral contact" would, however, be more descriptive since most of the calls are for direct referral. About 60 percent of these referrals were accepted. The telephone calls are handled by a professional staff person; one of the two staff members on the intake team.

The intake procedure has evolved to the recent exploratory practice of making it a two-step operation. The first step is the usual clarification of the presenting situation. The second step is to delay decision about the situation until the intake team has been able to consider various alternative approaches to the problem. This seems to allow for a more considered, less pressured disposition decision. The referring professional is contacted within a short time of his initial call. In those cases not accepted, alternative treatment plans or approaches are discussed.

From the patient's standpoint, the main result of the professional-referral policy has been the reduction of the period before a first appointment can be given. Currently, a family can be seen in about two weeks, or even immediately if there is an emergency. With another professional person in the community involved, the patient can be under continuing care and supervision during the waiting period.

From the Study Center standpoint, this policy has resulted in a considerable reduction in missed appointments. In addition, the information obtained from the referring person provides for greater flexibility and a broader range of approaches to the problems of the patient. The long range potential of this policy

is the provision for contacts and relationships with all of the allied professionals concerned with mental health. This means that other agencies are available for integration into a total program to approach a family's problem.

Who is the Patient?

Of the 150 cases opened last year, two-thirds concerned problems of children; these usually were referred by general practitioners or pupil personnel workers from the school. Typically, a case would be an elementary school boy who was exhibiting behavior disturbing to the school or his parents. This would probably be some type of disruptive behavior directed towards siblings or peers often with a lack of academic achievement.

The Center's focus frequently has been on the entire family rather than an individual identified as the patient. This focus would begin from the initial discussion during referral and would continue through termination of the family's visits. Approximately 300 to 400 people were seen during the year with this philosophy of involving the total "significant family." The significant family, of course, included the parents and their children, but at times, has also included foster parents, aunts, uncles, and one "family" currently includes the principal of the elementary school.

Although the first appointment could be the usual type of intake with the mother and father being seen by a social worker, it could have been done as a "family intake." The entire family would then be seen simultaneously by any staff member for an exploration of a problem as viewed by the various family members.

Treatment

Family Group Therapy is a treatment technique related to family intake. This has been discussed elsewhere in detail by Osberg (in preparation). To date some 40 families have been treated with this method. It is similar to family intake in which the entire family is seen together usually by one staff person. The major goal of the technique is to improve communication among family members. From the vantage point of the staff, there would generally be no sharp delineations between evaluation and treatment. We feel, along with many others, that

these two areas cannot be arbitrarily divided. At the end of 10 sessions or less, the family would usually have been terminated and probably returned to the referring person for continuing care. Another possible disposition might have been referral to an agency such as the Family Service Agency or the Health Department.

Other Treatment Techniques

A wide variety of other treatment techniques have been in use during the past year. These have included three groups of couples presenting overt marital problems. These marital-couple groups endured from a few months to a year. Another approach has been parent groups, and a separate group of problem children. This specifically concerned a group of parents and a group of their teen age children including both boys and girls.

A few people have been treated with individual psychotherapy and, at times, other members of the family have been seen collaboratively. These have tended to be rather long term cases with two being seen more than one hundred hours.

In Summary

We have continued to use the professional referral as a screening device and to utilize community resources. We have treated the family rather than a person using a short term, or, at times, a "crisis centered" approach. Considerable flexibility has been used in approaches to patients and families as well as in the use of staff members in a variety of roles far different from the traditional role of their discipline. Other allied professionals and agencies are involved wherever possible to form a more integrated approach to the mental health problems of a family or a community.

CONSULTATION ACTIVITIES

Consultation, as provided by the Study Center, refers to a diversity of activities with many specific goals. In all cases, however, the consultant advises, counsels, and deliberates with the consultee about particular problems.

What is Consultation?

Consultation may be thought of as a type of inter-personal

process. It has certain goals, and certain ways of achieving them. An aspect of mental health consultation regarded as crucial is the need for a continued relationship due, in part, to the fact that the consultant system exists over time in the community. The concept of system is an important one since both the consultant and the consultee operate in a relevant environment. The consultant must understand this well enough to help the consultee function more effectively.

The enabling function of the consultant is twofold. First, he brings new perspectives to bear on the system that might not be seen otherwise. Second, as an outsider, he may make observations and raise certain issues that a system member could not without jeopardizing his role.

The two main contributions of consultation can be summarized as helping the consultant (1) define the problem in proper perspective, and (2) consider management of it.

Types of Consultation

In the mental health field, consultation began around the individual case. Personal consultation, or clinical activity, attempted to help the patient solve a personal problem. Professional consultation (given to a professional consultee) was concerned with the diagnosis and disposition of individual cases. More recently, concern has shifted to the relevant environment of the individual, regarding this as important to consider as the person himself. It is thought that professional contact with the professional or resource persons in the community would be a better use of scarce talent and be more effective in preventive manipulations of the relevant environment.

Mental Health Study Center and Consultation

A major activity at the Study Center is professional consultation. The staff has been interested both in adapting traditional consultation methods to the needs in Prince George's County, and in developing different approaches that might be more productive.

Three main orientations encompass the Study Center's consultation activities: (1) case oriented, (2) program oriented, and (3) project oriented consultation.

Case oriented consultation is the process of talking with a consultee in regard to the management of a case. The consultant explores the view of the problem held by the consultee and the considered methods of management. Frequently, there is an attempt to change the perspective of the problem for the consultee and to enable him to continue to deal effectively with it.

Two programs best exemplify this activity; consultation to Pupil Personnel Workers (PPW's) of the school system, and to the Family Service Agency. The work with the PPW's has, in the past, been primarily a pre-referral screening. Frequently, the case has been brought with the hope of referral to the Study Center, and ultimately the transfer of responsibility. There has been some shift noted more recently toward discussing the case without thought of transferal. The contacts with the Family Service Agency more nearly personify traditional consultation. The Study Center consultants meet with them to consider their ongoing cases.

Diagnostic consultation is regularly offered to the Juvenile Court and has been used by the County Welfare Department. Not only does this meet a service need, but also provides a basis for future collaborative program planning.

In program oriented consultation, the consultant goes to the consultee agency to help with ongoing or proposed program areas. Consultation is offered to the school system in the following ways. Study Center staff members meet several times during the year with the PPW's and the Health Department to plan and evaluate the collaborative monthly seminar program. This seminar serves to bring together the entire PPW Department and staff representatives of the two mental health agencies in the County to discuss school mental health problems. The Nurse Aide's have made use of the Study Center staff to provide mental health information. This group has also made informal use of consultation from the Center's mental health nurse around specific problem cases.

The Study Center has a complex relationship with the County Health Department. The efforts of two Study Center consultants (a mental health nurse and a psychiatrist) are directed toward helping in the development of a broadened public health nursing program, and to maintain liaison with the Health Department's Mental Health Bureau.

Project oriented consultation is properly a special case of program oriented consultation. The problem to be faced and dealt with is usually relatively circumscribed and will involve time-limited contacts. Such consultation often takes two forms: (1) the provision of technical information or (2) the establishment of a collaborative activity.

The Health Department uses both types of relationships. A Public Health Service pediatrician working with the Health Department has met with Study Center staff members to discuss his project to evaluate the school health services. The Health Department has been developing a sizeable project to study ways of rehabilitating the alcoholic and his family. Study Center staff members have had contacts for over a year, and will probably finally collaborate with the Health Department on the evaluation phase.

A joint project with the school system, Department of Special Education, was begun about a year ago. The Study Center provided evaluations of the children and parents, regular home visits by the mental health nurse, a regular consultation contact with the teacher and principal of the class for the socially immature, and a discussion group for the parents of the children in the special class. This project has been a demonstration activity and will eventually lead, it is hoped, into a continued relationship with the Special Education Department of the school system.

National Consultation

The Study Center often provides consultation on various aspects of community mental health to the professional groups throughout the United States. For example, state and local groups use staff members in a consultative capacity for workshops, conferences, and Technical Assistance Projects.

In Summary

The above discussion demonstrates the complexity of the contacts by the Study Center with the community. They do not fall into any one of the three categories, but must be described as a combination of multi-purpose consultation, and collaboration on cases or programs. Considerable effort is still expended both in the community and with well known consultee groups to provide education as well as consultation. Education (sharing

of information), however, must be regarded as integral in meeting the consultee "where he is," and then in the development and maintenance of a firm consultative relationship.

RESEARCH AND EVALUATION

General Considerations

In order to accomplish the mission of being a demonstration unit which develops "model" activities, the Study Center must constantly look at itself, community relationships, and its problems. Among these problems, the execution and completion of research and evaluation activities in a setting committed to service activities remains a challenge. The maintenance of balance between service and research activities becomes more difficult when the services themselves are accompanied by high standards of critical evaluation.

From the clinical standpoint, the service policies of the Study Center first came under the scrutiny of evaluation, with resultant changes in emphasis on who was seen as the patient, criteria for acceptance, and type of service offered. This spirit continues to be exemplified by the adoption of exploratory activities with built-in provision for periodic evaluation. As the program has developed, however, a research focus has been brought to bear on cooperative demonstrations with other county agencies and on discrete mental health projects pursued by Study Center staff.

Research and Program Development in the Community

Research activities carried out by an agency in the community carry certain obligations and responsibilities not usually encountered by discrete, more isolated projects. Most important is the establishment and maintenance of working relationships so that the agency is able to continue in the community. The working relationships around the research are of a collaborative nature, and involve material sharing of information. The community, through the participants, gives the agency cooperation and information. This obligates the researcher to give, in turn, cooperation and information. Very often this side of the "bargain" is not fulfilled. It becomes a very knotty problem of how to inform the participants and the community-at-large what is going on, and, further, how the results may be useful to them. The community must be made to understand that it is regarded as

a collaborator, not as a "guinea pig" to have its secrets exposed.

In this connection, the subtle processes involved in fashioning programs to community needs in and with the collaboration of other agencies are pertinent. The Study Center continues this activity as it has in the past when the Study Center, its Advisory Board, and the Mental Health Society cooperatively stimulated the creation of a mental health clinic within the County Health Department. At present, the close liaison with the Health Department, has led to the development of a demonstration in the public health approach to alcoholism, centered in the Bureau of Mental Health of the Health Department. Currently, two members of our staff have been instrumental in assisting the Health Department develop a tool for the evaluation of this program in alcoholism. Specifically, interest focuses on the personal and sociological characteristics of people who accept the treatment program when it is offered as opposed to those who do not accept it. The same staff members involved in this technical advisory aspect of our relationship to the alcoholism project are also concerned with documenting the very processes of consultation involved in this relationship. Our concern is not only with the developmental course of this particular demonstration project, but with the initiation and maintenance of such projects in general.

Similarly, as a demonstration of possible mental health center functions in a community, we are monitoring and documenting our developing relationship with the Police Department, currently manifested in a projected seminar for juvenile officers. Ostensibly the seminar is designed to transmit mental health concepts to juvenile officers in an informal discussion group setting. Actually, however, it is anticipated that the focus of this group will be on the definition of the role image of the juvenile officer, his function in the community and his relationship to the rest of the department. The development and nurture of a relationship between the Study Center and the Police Department is of general interest, especially in light of a current prevalent view that the two agencies represent diametrically opposed philosophies.

Examination of Consultation to Community Agents

To "combat" mental health problems in the community, the Center searches for new ways of dealing with various problems of deviancy. Attempts are made to assist other professionals and

interested persons in the community to assume responsibility for handling mental health problems. Consultation to the pupil personnel workers, police, welfare workers, Family Service Agency staff is directed toward increasing their effectiveness in handling mental health problems and utilizing community resources.

At the present time, we are in the process of evaluating the consultation program with PPW's. It is hoped that this evaluation will offer some leads toward understanding consultation activities with other agencies.

Research within an Agency

In addition to the maintenance of a proper balance of activities within the agency, and the maintenance of community collaboration, there is the issue of the location and nature of responsibility within the agency system to ensure that research activities get carried out properly. The major concern often lies in the fact that the research endeavors may result in an engulfment of the remainder of agency activities, and thus lead to restraints of activity and exploitation of other's efforts. Much of this resides in the present over-emphasis of "pure research" professionally. In order to ensure that any activity is accomplished within an agency, it is imperative that these issues be effectively resolved.

Mental Health Study Center and Research Activities

The Study Center continues to be a setting for examination of issues pertinent to the administration and performance of mental health research activities. The project "The Epidemiological Study of Reading Ability," a six year cohort project of 3000 school children, is a valuable illustration. Since the originators of the project (initiated in 1954) have left the Study Center, it has meant that the new staff has had to assume responsibility for the project. One of the early problems that the present staff has been attempting to resolve is the administrative and manpower problem encountered when planning long range studies in a service setting. A study group was created, with a temporary project director, which set about to review past data analyses, and staff papers concerning the project during the past six years. So far, basic information on the cohort has been coded and prepared for electronic data processing. A revised draft of the project proposal which is now being prepared has been oriented to incorporate portions of the original design as

well as to include specific interests of the current staff. The project goal has been specified to examine the relationship of early reading performance with subsequent academic and social adjustment.

TRAINING

Broadly, training can be seen as a continuum. One extreme is described as informal; that is, knowledge obtained from practical on-the-job experience. The other extreme is formal training which is embodied in a definite curriculum and often implies both university affiliation and accreditation.

Of equal concern as the type of training, is who is being trained. The teacher is always taught by those whom he teaches. The student may be the lay person who is being "educated," or the professional who is being "trained." The former most often refers to the acquisition of knowledge, the latter, of skills.

Study Center and Training

At the present time a limited amount of training is carried on at the Study Center. However, there are three specific training activities which are of interest.

COSTEP program. The Public Health Service Commissioned Officer Student Training and Extern Program has provided two graduate students in social science to participate in the Study Center's research program. This past summer these students developed a research project to relate birth order to reading ability. It is to be hoped that the COSTEP students will become an integral part of the Study Center's program of training and research.

Mental health counselors. The Study Center is cooperating with the Adult Psychiatry Branch in training mental health counselors who are sensitive, mature women with no formal mental health training. They are part of a program exploring the development of new types of mental health personnel. Two counselors are receiving training in the interviewing of patients.

Seminars. Consultation with the Family Service Agency is occasionally formalized into a discussion seminar. A recent meeting was devoted to the topic "Problems and Techniques in Family Group Therapy and Joint Interviews." Several workers

from the Montgomery County Family Service Agency attended.

A Study Center staff seminar is held weekly to discuss, systematically, areas of interest. Some recent topics have included mental health surveys, use of routinely collected community data and problems involved in community research.

Short-term Training

During the past year a number of professional persons have visited the Study Center for periods of time ranging from one to ten days. Among these individuals have been physicians, educators, nurses, and mental health personnel interested in the mental health activities in Prince George's County. Although considerable staff time is utilized in programming these visits, this is considered to be consistent with our role as a demonstration unit.

III. THE FUTURE

Having described briefly our history, our setting and our present program activities, we would now like to look ahead. We see many opportunities in each of our areas of interest. Convinced that we must maintain the trusting relationship with other agencies in Prince George's County, we propose to strengthen our clinical services both in terms of rendering services and in terms of an evaluation of the effectiveness of the services. In our relationships with other agencies, we are in the process of studying consultation and look forward to the possible extension to other agencies of the kind of cooperative project inherent in the study of alcoholism sponsored with the Health Department. We suspect that a comparable project in the area of delinquency may be in the offing.

Most challenging and stimulating is our new mission implicit in our transfer to the area of program development in the National Institute of Mental Health. Of primary importance we see the opportunity to provide leadership in the theory, practice and research in community mental health. This requires a consideration and communication of basic issues and current concepts, the application and evaluation of service methods and the development and application of methods of community mental health research. These considerations arise from our unique position as the Institute's community-based mental health resource.

At the present time, our team consists of representatives of four mental health disciplines - psychiatry, psychology, psychiatric social work, and mental health nursing. In a broader sense, this team is augmented by our Advisory Board and by consultants in child psychiatry, epidemiology and group psychotherapy. Looking to the future, there are a number of questions that arise.

From the standpoint of the staff:

What is the most effective role for representatives of each discipline?

How much time and energy should be devoted to specific services to patients, to consultation, to research, to training?

What types and at what levels should training be provided?

Should training be limited to service personnel or should it be broadened to include affiliation with academic institutions?

How may the balance between research and service be maintained?

From the standpoint of the community and its Advisory Board:

What should be the nature and function of an advisory board?

What, the role of its members?

As an agency engages increasingly in research, is a technical advisory board with representatives from specific agencies with specific skills preferable to a board more broadly representative of the community?

From the standpoint of consultants:

How much knowledge of a unit's operation should a consultant have to be optimally effective?

Should he consult only around specific issues or also around program goals and philosophy?

We enumerate these questions not only to indicate that they are perplexing but also to add that they are faced to a certain extent by any community mental health agency.

In order to attempt to get answers to these questions, there are a number of prerequisites, some intangible, some tangible. Among the latter, we include the needs for additional staff and an enlarged facility. We are planning to augment our present staff by several professionals including a social scientist, a psychiatric social worker and psychiatrist who will give

us depth in programming. At present we are negotiating to enlarge our physical facility. Less easily accomplished is the necessity of developing and maintaining a stable staff so as to provide continuity in our program.

In conclusion, in this report we have aimed not only to present our roots, our present involvement in program activities but also our thoughts about the future. In doing this we have tried to convey not only facts and figures but also something of the breath and spirit of our organization.

APPENDIX I

STAFF - MENTAL HEALTH STUDY CENTER

Professional

Miss Dorothy Boone	Mental Health Nurse
Dr. Bertram S. Brown	Staff Psychiatrist
Mrs. Diane J. Fine	Research Assistant
*Dr. Arden A. Flint	Former Associate Director
Dr. Ferdinand R. Hassler	Clinical Director
Dr. James G. Kelly	Staff Psychologist
Mr. Perry Levinson	COSTEP
Dr. Fortune V. Mannino	Staff Psychiatric Social Worker
**Dr. David P. Michener	Former Clinical Director
Dr. John R. Newbrough	Staff Psychologist
Dr. James W. Osberg	Director
Mr. Herbert L. Rooney	Associate Director
Mrs. Mae E. Rosenberg	Social Science Analyst
Mrs. Grace L. Schoner	Staff Psychiatric Social Worker
Dr. Robert S. Shellow	Staff Psychologist
Mr. Charles D. Ward	COSTEP
***Dr. Stanley F. Yolles	Former Director

*Now with the Biosocial Growth Center, CI, NIMH
**Now in training status at Johns Hopkins University, School of Hygiene and Public Health
***Now Associate Director for Extramural Programs, NIMH

Consultants

Dr. Reginald S. Lourie	Child Psychiatry
Dr. Beryce W. MacLennan	Group Psychotherapy
Dr. Raymond Seltser	Epidemiology

Secretarial and Clerical

Mr. Bradley W. Becker	Mrs. Helen Piltch
Mrs. M. Virginia Garrity	Mrs. Shirley E. Robinson
Mrs. Lucile B. Gosnell	Mrs. Marie P. Schwarz
Mrs. Rose H. Landsman	Mrs. Christine M. Wodoslawsky
Mrs. Lillian S. Oksner	

APPENDIX II

ADVISORY BOARD - MENTAL HEALTH STUDY CENTER

Mrs. Reuben Spellman - Chairman, 1960-61
Dr. Albert Roth - Vice Chairman, 1960-61
Mr. Victor Rice - Chairman 1959-60

Mr. William R. Ahrendt	Business and Industry	1958-61
Mr. Doswell Brooks	Negro Community	1959-61
Mrs. Charles Edelson	League Women Voters	1960-61
Dr. Murray Grant	County Health Officer	Ex-Officio
Mr. John S. Hewins	Park & Planning Commission	1959-62
Mr. Stanley Jacobson	Board of Education	1960-63
Dr. Joyce Gale Klein	Family Service Agency	1960-62
Dr. Thomas Magoon	University of Maryland	1960-63
Mrs. Dorothy McArdle	Prince George's Gen. Hosp.	1960-63
Dr. Albert Roth	County Medical Society	1959-62
Mrs. Reuben Spellman	County Council of PTA	1958-61
Rabbi Chaim Williamowsky	Religious Organization	1959-62
*Dr. Dorothy Mohr	University of Maryland	1958-60
*Mr. Victor Rice	Board of Education	1957-60
*Mr. Thomas Ritchie	Prince George's Gen. Hosp.	1957-60
*Mrs. Carolyn Wynne	Soroptomist Club	1957-60

*Terms Expired September 1960

ANNUAL REPORT OF THE PROFESSIONAL SERVICES BRANCH, NIMH

CALENDAR YEAR 1960

The Professional Services Branch continued to fulfill its function in relation to program development activities, especially through pilot research projects, and to perform a variety of staff and consultation functions to the Office of the Director and the Institute as a whole.

A major development was the formation of the Special Grants Review Committee. This Committee reviews all Special Grant applications and makes recommendations to the National Advisory Mental Health Council. It also serves as a consultant group to the Professional Services Branch and other members of the staff of the Institute. In this connection it discusses current projects with the principal investigators and appropriate staff members where no additional funds are requested and no formal recommendations are required, and it assists in the development of new areas.

Dr. Denise Kandel completed her special assignment in the Branch and has moved to Boston where she holds a postdoctoral research fellowship at the Massachusetts Mental Health Center. Mr. Derek Roemer and Mrs. Rasma Finlayson have joined the staff on a temporary basis to assist the staff in special studies of juvenile delinquency and of the role of mental health and other public health programs, respectively.

Studies Concerned with the Prevention or Reduction of Disability in Pathologic or Deviant Populations

Rehabilitation

Dr. Ralph Notman, principal investigator, and Dr. Richard H. Williams have continued to work on a book analyzing the Boston State Hospital Pilot Study in Rehabilitation and Rehabilitation Personnel. The extensive analysis of background data concerning the patient population as a whole has been completed. A new outline has been prepared and parts of the manuscript are in draft form.

Dr. Simmons and his group at the Harvard School of Public Health have completed the data gathering in a special study in which relatives of 650 patients, leaving mental hospitals in the Boston area and its hinterland, have been interviewed, at time of discharge and at time of rehospitalization, or one year after discharge. Analysis of the data is in progress. The Hogg Foundation has published After Hospitalization: The Mental Patient and His Family, summarizing the work of this project to date.

Dr. Kandel has completed her analysis of the 49 projects represented at the conference on studies in psychiatric rehabilitation held in June 1959. Dr. Williams is continuing the analysis, for publication of the book on problems of research and demonstration in this field.

A study directed by Dr. Harold Sampson of the California Department of Mental Hygiene, has gathered intensive and extensive information about the careers of members of seventeen marital families in which the wives have been placed in, and then released from, a State mental hospital. The wives are white, under forty years of age and living with their husbands at admission, without previous hospitalization for mental illness, and have a dependent child in the home. They were sequentially admitted to the State hospital during late 1957 and early 1958 and there diagnosed as schizophrenic.

Wives and husbands were regularly and frequently interviewed from the time of the wives' admissions up to 100 weeks following their releases. This resulted in an average of fifty wife and/or husband interviews per case. Relatives, community persons involved in the cases, and hospital personnel were also interviewed one or more times. Records were abstracted from many sources. Family interaction and hospital procedures were subject to intensive observation.

Analysis and write-up are now in progress. The aims are to contribute to the social psychology of personal disorganization, to the understanding of the structure and functions of modern marital families, and to the understanding of currently institutionalized processes of control of deviant conduct.

Mental Retardation

The Branch has developed four major projects in the field of mental retardation during the past six years. They have made a significant impact on the field. The goal of these activities of the Professional Services Branch has been essentially achieved, and the activities of the Branch have diminished markedly. Within a short time, all program activities will be in the relevant branches of the Institute and not the Professional Services Branch.

The American Association on Mental Deficiency project on "Technical Planning in Mental Retardation" has resulted in an increase in program planning and development of the field. Many of the activities started by this project are now being taken over as regular functions of the AAMD or by other organizations in the field. One measure of the impact of this project is the increase in research grants, training grants and service programs supported by the National Institute of Mental Health, States and foundations.

The Pacific State Hospital study of the impact of institutionalization of the mentally retarded has finished its third year. Several reports and papers have been presented at national meetings and published in professional journals. Other proposals from the State of California and elsewhere have arisen from the work of this group.

Juvenile Delinquency

Several special grant projects in juvenile delinquency have been under way during 1960, with Dr. Raymond Gould as the Branch liaison person. One project, at the South Shore Courts Clinic in Quincy, Massachusetts, concentrated in its pilot phase on developing a typology of a sample of 50 delinquents who came to the juvenile court in 1957. This typology was designed so as to be relevant for treatment purposes. The study included the design of an extensive schedule for accomplishing the social and psychiatric diagnostic study and has involved reliability checks on the observations of the psychiatrist by one or more other psychiatrists. It has also included a specification of the ideal treatment, the recommended treatment, and the actual treatment or disposition prescribed by the court, with predictions regarding the probability of recidivism in each instance. This group received a continuation grant of 3 years' duration in 1958. This continuation project involves enlarging the sample to permit more refined analysis and intensive follow-up so as to test the predictions and deepen the diagnostic understanding of the cases. Instruments for assessing physical health, for psychiatric diagnosis, psychological and social diagnosis have been designed and are being administered to a sample of 100 cases. The Clinic staff is also preparing a design for an experimental treatment phase on a community-wide basis, and will apply for funds for this purpose in 1961.

A second project, with Drs. Lippitt and Withey at the University of Michigan, has completed its pilot phase using a social psychological approach to develop a clinically meaningful typology of delinquents with a focus on the social situation of the child as well as on significant attributes of the child and his family. They have also conducted pilot investigations of significant agencies in the community, such as police, juvenile courts, social agencies, and schools, and are completing a study of a sample of Negro delinquents and of girl delinquents. They have been given support for a demonstration or field experiment phase on a community-wide basis which is currently under way.

Dr. Isidor Chein has been supported in a small project to explore the feasibility of a large-scale delinquency and drug addiction control project in a high-delinquency area of New York City. This exploration led to the development of a large-scale action project under the auspices of the Research Center of the New York School of Social Work at Columbia University, and of the Lower East Side Neighborhood Association in New York City. In addition, in November 1960, the National Advisory Mental Health Council approved support for a large-scale epidemiological study of delinquency in New York City. This study, designed by Dr. Chein, may supply valuable evaluation tools for delinquency projects or for any planned change effort in such fields as venereal disease control, alcoholism, preventive mental health care, etc.

A report was submitted to Congress as requested by the Appropriations Committees of the House and of the Senate. The request was for "a most careful and thoughtful study of what can and should be done about delinquency in the future." This study was the full-time concern of Dr. Gould, Dr. Cook, and several full- and part-time NIMH staff members from the spring of 1959

to the spring of 1960. They were assisted in the preparation of extensive working papers by the staff of the Judge Baker Guidance Center and the Thom Clinic of Boston, and the South Shore Guidance Center of Quincy, Massachusetts. In addition, Dr. Nicholas Hobbs of Peabody College made a short visit to France in order to investigate French methods of delinquency control and training of delinquency personnel which were reported as being highly successful. Judge Mary Conway Kohler of New York City also gave valuable consultant service to this project and contributed papers on European programs and on community organization methods in New York City and other parts of the United States. The NIMH collaborated with the Children's Bureau on this report. For the first time, Congress earmarked $1 million for delinquency research, demonstration, and training projects in the fiscal 1961 budget for the NIMH.

In addition to supporting special grants of various kinds in the field of juvenile delinquency, Branch members have become engaged in activities designed to clarify the nature of a number of problems, and the status of current research and demonstration programs in this field. The main activities now in progress are:

1. A number of appendices of the Report to the Congress on Juvenile Delinquency have been edited, revised, and are being reproduced for distribution on a limited scale to interested professionals in the field. Appendix II of this report, "An Assessment of Current Mental Health and Social Science Knowledge Concerning Juvenile Delinquency" is, in addition, being extensively revised and expanded for eventual publication through regular publishing channels.

2. A list of research supported by the National Institute of Mental Health most relevant to the field of juvenile delinquency is being prepared for general distribution. This work is being done in collaboration with the Research Grants and Fellowships Branch and the Community Services Branch (in relation to Mental Health Project Grants). The research and demonstration projects in this list will be presented in an analytical classification which will allow other researchers and students to appreciate the general nature of the research or project undertaken (principal investigators and institutional addresses will be listed to facilitate intercommunication, but no summaries of results will be given).

3. Liaison has been established with two organizations active in the field of delinquency, the National Council on Crime and Delinquency (formerly the National Probation and Parole Association), and the Special Youth Program of the Ford Foundation. Preliminary discussion has indicated two possible areas in which joint cooperation may be worthwhile at this time: (a) the preparation of an index of current community programs over the United States, regardless of source of support, and (b) the provision of lines of communication to establish a mutual research clearing house. This second activity has already been undertaken by the NCCD under a grant from the Ford Foundation and it may be that they will remain the central repository of research information.

4. A small seminar has been inaugurated with participants from several Branches or Laboratories of the NIMH, having strong active interest in research

or theory in the area of juvenile delinquency. The functions of the seminar are to discuss the codification of research and theory discussed above, to identify promising areas for further work, and to plan several larger conferences, to which various experts would be invited, organized around key issues of theory having implications for research. It is planned that the proceedings of these larger conferences will be made available for wide distribution.

5. Consultation has been provided to the newly formed subcommittee on juvenile delinquency of the Committee on Children, of the American Psychiatric Association. Recent materials in the field of delinquency have been made available to members of this group and continuing consultation is planned as they, in turn, formulate policy concerning the role of psychiatry in juvenile delinquency.

The Usage of Alcohol

Work in the field of alcoholism is still a major activity of the Branch. There are four special grants designed to develop and extend work in this area. These activities should result in increases in training and research grants and in new service programs throughout the country. It is unlikely, therefore, that additional extensive work by the Professional Services Branch will be started.

Of special importance is the progress made toward the establishment of a Cooperative Commission on the Study of Alcoholism. Dr. Nevitt Sanford, Professor of Psychology at the University of California and currently at the Center for Advanced Study in the Behavioral Sciences, Stanford University, has been appointed Scientific Director of the project. Although preliminary work is under way, the major program awaits the final constitution of the Commission and the recruitment of the staff. The project will undertake a complete review and evaluation of the many facets of alcoholism. Several task forces will be formed to investigate specific areas. The Scientific Director will assume responsibility for the over-all direction of the work which, in turn, will provide material for a major, long-term university study of problems related to the use of alcohol.

The study of normal drinking practices is proceeding satisfactorily. Under the direction of Dr. Ira H. Cisin various interviewing techniques and schedules have been tested. A major pre-test effort is currently in the field. The purpose of this project is to develop instruments for gathering data about nonpathological alcohol consumption. It is essential that such data be gathered if a baseline from which to measure deviation in drinking patterns is to be established. This special grant is located in the Division of Alcoholic Rehabilitation of the California State Department of Public Health.

A third study deals with the values and habits surrounding alcohol usage as they are influenced by the cultural factors of various ethnic groups. This study is being conducted in Colorado, and Dr. Thomas Gladwin of the Community Services Branch is the liaison person from the National Institute of Mental Health.

The fourth study is intended to clarify the confused state of terminology in the field of alcoholism. It will also recommend a nomenclature which will be useful for research and treatment. Mark Keller of the Yale Center of Alcohol Studies has replaced John R. Seeley as principal investigator.

The Branch and the Division of Special Health Services, Bureau of State Services, have been cooperating in the field of traffic safety. Of especial concern has been the relationship between alcohol consumption and automobile accidents. A series of small working conferences has been completed. The series included discussions of the psychological and physiological effects of alcohol ingestion, law enforcement problems, adequacy of mortality and morbidity statistics, social-psychological factors, and educational and mass motivational techniques. Plans are currently underway for a National Conference on this problem.

Dr. Duhl has been the liaison person for the Cooperative Commission and the nomenclature study, and Dr. James H. Fox has performed this function for the normal drinking practices study and the drinking-driving conferences.

Suicide

Drs. Duhl and Fox are reviewing and evaluating the work in the field of suicide. The Branch's activities are, therefore, in their early stages. One special grant has been made to Dr. Louis I. Dublin. He is engaging in a demographic and epidemiological study. His work will assist the Branch in its plans for program development in suicide.

Studies of Fundamental Processes Affecting the Mental Health of Populations of Entire Communities (Local, State and National)

Communication of Mental Health Concepts

The major study of communication of mental health concepts, under the direction of Drs. Nunnally and Osgood at the University of Illinois, has been completed, and a book is in press.

Child-Rearing Practices and Beliefs -- The Parental Role

During the fourth and final year of the project on the Communication of Information about Child Care and Development, under the direction of Drs. Sears and Schramm at Stanford University, it is planned to complete all work. This involves completing the analysis of all studies and the final writing of research reports. Much of the preliminary analysis and write-up of the work has already been done, but follow-up data on two major studies--the San Francisco Critical Period Study and the San Jose General Communication Study--collected in the spring of 1960 are still in the analysis stage. In addition to the completion of these data analyses, it is planned to carry out one additional study on the effect of distance between the position advocated in a communication and the position originally held by a parent on child rearing. In this study, it is planned to use communicators who vary in prestige. The theory is that distance increases dissonance. When low

prestige communicators are used, discrediting the source is available for dissonance reduction. This method is closed off when high prestige communicators are used. Thus with a high prestige source distance should give rise to more change, but not with a low prestige communicator. The data on this point are thus far equivocal and previous research by others has provided apparently contradictory findings. Finally, it is planned to integrate all studies into one final monograph report.

Data collection and analysis are continuing in the study of the personality developments of 97 adopted children, being conducted under the direction of Dr. Leon Yarrow in the Greater Washington Area with the cooperation of six social agencies. This study is concerned with the significance for personality development of a change in mother-figure during infancy. The major variables are the developmental stage at which the change occurs, the quality and depth of mother-infant relationship preceding and following the change. The theoretical background of the study derives from two sources: psychodynamic theories of the role of early object relationships for personality development, and the biological theory of specific vulnerability of the organism to deprivation or trauma during critical developmental phases. The situation of adoptive placement, involving change from foster to adoptive mothers, provides the natural setting. Subjects are 80 cases referred at birth, and then placed in adoptive homes at ages ranging from 5 days to 12 months. This is a longitudinal investigation involving direct study of infants and their psychological environment, beginning in the first month of life and continuing over a five year period. Data are obtained by infant observations, developmental tests, and interviews in the foster and adoptive homes monthly during the first six months, then at three month intervals. Projective techniques, intelligence tests, and group observations are used after the infancy period.

Aging

A sixth wave of interviewing has been completed in the Kansas City Study of Social and Psychological Aspects in Successful Aging, under the direction of Dr. Henry of the University of Chicago, and a seventh wave is under way. The first major report of the study has been completed in book form and accepted for publication by Basic Books. The provisional title is The Process of Growing Old. It is by Drs. Elaine Cumming, William Henry, and others, and will contain a Foreword by Professor Talcott Parsons of Harvard and a Preface by Dr. Williams.

An international research seminar on social and psychological aspects of aging was sponsored by a special grant and held in Berkeley in August, with approximately 80 participants. Proceedings will be edited and published in book form. Drs. Williams, Havighurst and Neugarten presented papers based on the Kansas City Study.

The final draft of the manuscript of a book reporting the Study of Retirement by the late Else Frenkel-Brunswik and staff at the University of California, has been completed.

The Study of First Admissions to Mental Hospitals in San Francisco, under the direction of Dr. Simon and Mrs. Lowenthal, has made notable progress. Some 600 hospital cases and 600 persons living in the community have been studied by interview with themselves and other members of the family, by tests and examinations. The project was voted additional funds by the Council to provide for follow-up studies of both groups. Papers were presented by several members of the staff at the Seminar and at the Fifth International Gerontological Congress in August.

The Utilization of Space

The Branch continues interest in the physical and social environment as it relates to mental health, through meetings of a group of informal consultants from various disciplines. Out of discussions in this group have arisen several projects which we have supported. For example, a study of the West End, an urban slum community in Boston, is being made to determine the impact of the crisis of slum clearance upon the population. Results are suggesting the kinds of services required to aid in resolving such crises. In addition, this project offers the opportunity for a community laboratory for training persons in public health and community psychiatry. It is interesting to note that people in the field of planning look to this project as the main study in the United States dealing with urban renewal.

Positive Aspects of Mental Health

Dr. Lauren Wispé has undertaken to survey the literature pertaining to positive aspects of mental health, paying attention especially to two factors: (1) what have been the dispositions of the major theories and the empirical findings about personality factors in scientific and artistic creativity, and (2) since presently so many artists and scientists work in large organizational settings, what are the social conditions conducive to the development of creative impulse? In addition to the considerations above, two other problems present themselves. The first raises the question about the relationship, if any, between the factors in sound mental health and the expression of the creative impulse. Dr. Wispé is presently preparing a paper on the "Continuity Principle" which explores this problem further. The second problem concerns itself with the impact of the various educational institutions upon artistic creativity and scientific productivity. A number of popular books are available, but there are only a few controlled studies of this important aspect of positive mental health.

Although a considerable amount of information has been gathered about pathogens in our culture, there is a dearth of systematically derived information about the more creative segment of the population. Particularly lacking have been investigations of outstanding scientists. With this in mind, Dr. Wispé undertook a survey of 100 outstanding behavioral scientists, and a control group of the same size. This is a unique set of data, since it is one of the few, if not the only, study in which certain personality factors, important institutional influences, and the creative output of the outstanding scientists may be compared with a carefully selected control group, and certain hypotheses formulated. Dr. Wispé is currently concluding his analysis of these data, and has already presented several papers on the findings, the most recent being an article in Adult Leadership for June 1960.

In a second portion of this same study, fifteen publicly controlled and fifteen privately financed universities, all with record productions of eminent scientists, are being compared. These data have not yet been completely analyzed, but suggest important differences between the most-eminent-producing universities and the others.

Psychophysiological Changes in Creative Social Groups

Recent developments in psychophysiology, and in polygraph recordings, suggest that certain measurements may be obtainable from individuals engaged in social situations where they are attempting to solve problems, collaborate in writing a story, etc. Dr. Wispe' is currently considering the applications of some of these devices with Dr. Albert Ax of the Lafayette Clinic. This is very much in the developmental stage, but if instruments can be utilized in such an enterprise, exciting possibilities exist for learning more about the basic psychophysiology of creative mental processes.

Studies of Fundamental Processes Affecting the Mental Health of Specific Populations in Organizational Settings

Mental Health in the School

The Branch's interest in the study of mental health in the school and college continues through its project at the Bank Street College of Education and with its grants to Harvard and to the University of Michigan for the study of colleges and their impact on students. These three projects have had an important impact on other work going on in this field. Close collaboration between these groups and other workers in the field through conferences, consultation and professional reports has stimulated a tremendous amount of activity. There has been continued contact with the Social Science Research Council Committee on Adolescence and other groups concerned with the same problem.

Preliminary negotiations for the development of a new program of residential treatment programs for disturbed children have continued. It is hoped by means of this work that we will get a clearer picture of what might be available to us in making our limited resources available to a greater number of people in this and other mental health areas. This program is pending and should be under way within the next several months.

New Methods of Instruction

The last few years have seen remarkable developments in the application of experimental psychology to methods of instruction. The new field of programmed learning and auto-instructional devices (popularly known as "teaching machines") has implications for mental health interests in addition to their central educational significance.

1. A number of mental health problems centering around the school situation (counseling, testing, classroom discipline and others) arise from the immediate as well as the long run effects of weak instructional methods,

large ratio of students to teachers, etc. It is likely that the development of an effective instructional technology which can by-pass these problems will restructure the nature of clinical consultation, testing, and other problems in the school.

2. Auto-instruction has great potential importance in the training of professional specialists. For example, research is now under way (supported by the Carnegie Foundation) on the feasibility of automating instruction for large segments of medical education.

3. Possibilities exist in the development of instructional programs for special populations: the retarded, children with learning blocks, educationally deprived children, such as lower class delinquents (who are also intolerant of the student-teacher relation). In general an optimal instructional technology invites re-examination of many classic issues of psychology, the nature-nurture problem, the interaction of emotional disturbance and educational retardation, and the relation between measures of aptitude and achievement. It suggests the possibility of new strategies for more effective blends of teaching, diagnosis, and therapy--operations very difficult to separate when dealing with the young.

Dr. Cook is undertaking a general analysis of the rapidly developing research and development in the field of programmed learning or auto-instruction. A survey report on this field is in preparation and will soon be available for distribution within NIMH. Explorations are under way aimed at encouraging grants which would study adaptations of the method of teaching machines for various disturbed or deviant populations.

Mental Health in Work Groups

The project under the direction of Dr. Chris Argyris of the Department of Industrial Administration at Yale University was designed to investigate the observation that the needs of the individual worker tend to be in conflict with the needs and policies of the work organization, and to conceptualize and develop measures for optimum mental health of the worker. The first phase of this study was completed during 1959 and resulted in a book entitled Understanding Organizational Behavior, Dorsey Press, Homewood, Ill., 1960, and in articles in several journals such as The Administrative Science Quarterly. A follow-up study, being designed by Dr. Argyris, was approved by the National Advisory Mental Health Council in November 1960. This study will permit the designing and pilot phase of a field experiment in optimizing individual and organizational health, and will permit the development of a new contribution in the theory of the mental health of work groups.

The study directed by Drs. French, Kahn, and Mann at the University of Michigan developed a theory of the dynamics of work organizations which was expressed in a book-size report to NIMH. This report, and the work of Dr. Argyris, was discussed in a 3-day conference at Ann Arbor, Michigan, in the spring of 1960, with Dr. Argyris participating. As was anticipated, this study resulted in the submission of several applications to NIMH for support of specific research projects. Three of these, one on the effects of automation, one on the effects of role conflicts, and another on the mental health problems of shift work were under way as regular grants during 1960. Other

applications, one in the area of psychosomatic illnesses which appear to be brought on in the work situation, are pending. Dr. Gould continued as liaison with projects in this area. He presented a paper before a TVA conference on industrial morale in April 1960. Excerpts from this talk were published in Volts and Jolts, a monthly publication of the TVA. Informal relationships have continued between the research workers in these projects and those in the area of college mental health.

Studies of the Mental Health Aspects of Traumatic or Stressful Events in Various Populations

Disasters

No new activities were begun in this field during the past year.

Epidemics

No new activities were begun in this field during the past year.

Accident Prevention

Dr. Bernard H. Fox, assigned to the Accident Prevention Program, Bureau of State Services, left the Public Health Service to become the head of a new laboratory of psychology. No replacement has as yet been found for him. He has continued to cooperate with the Branch, especially in relation to the conferences on drinking and driving, with Dr. James H. Fox (see under The Usage of Alcohol, above).

Other Activities

Dr. Williams has continued to serve as a consultant to the Group for the Advancement of Psychiatry. He has recently been requested to serve as staff coordinator for the Ad Hoc Committee on Mental Health and Public Health established by the Surgeon General and will be responsible for preparing drafts of the Committee's report. He is also directing a study of the role of the social and behavioral sciences in public health.

Dr. Duhl, who is on the Executive Committee of the American Public Health Association Program Area Committee on Mental Health, has aided in the preparation of the report entitled "Guide to Control Methods and Mental Disorders" which will be published in the near future. In addition, he has continued to work with the Group for the Advancement of Psychiatry and numerous other organizations.

Dr. Gould presented several papers on juvenile delinquency. He spoke before the First Annual Conference on Juvenile Delinquency at the Children's Center in Laurel, Maryland; the National Association of Training Schools and Juvenile Agencies in Atlantic City, New Jersey; the Annual Training Institute for Southern Juvenile Court Judges in Blue Ridge, North Carolina; and Hawaii's "White House" Conference on Children and Youth in Honolulu. Other

talks which were or are being published include "Delinquency and the Public Welfare," which appeared in the September 1960 issue of Public Welfare, and "Juvenile Crime and Aid as Seen from the Mental Health Viewpoint," to appear in the December 1960 issue of The Journal of the American Osteopathic Association.

He also continued his activities as a liaison with the field of social work, particularly in the research area. He served on the Board of the Council on Social Work Education and on the Research Committee of that organization. He also served as the secretary of the Executive Committee of the Research Section of the National Association of Social Workers, on the Commission on Social Work Practice of that organization, on the Executive Committee of the D. C. Chapter of the National Association of Social Workers, and on the Committee on Children and Youth of the American Public Welfare Association. He also had some contacts with social work organizations which were preparing to submit research applications.

Dr. Wispe' and Dr. Jay Jackson of the University of Kansas have been exploring the possibility of convening a group of behavioral scientists to explore the various avenues of behavior science theory and knowledge to see in what manner they can best contribute to the field of mental health. Dr. Nathan Cohen, Dean of the Applied Social Sciences School, Western Reserve University, is also interested in this problem. Various scientists, especially in the fields of sociology, social psychology, psychology and anthropology will be contacted, to see if an interest exists, and whether a set of original papers can be contributed. A two-day conference might be arranged with the results of the discussion as well as the original papers to be published.

Conclusions

The Branch has initiated discussions of ways to improve the process of program development, including attention to selection of areas, types of activities and ways in which the Branch can assist the Institute as a whole. These discussions will continue in 1961, and will involve the Special Grants Review Committee.

PUBLICATIONS AND REPORTS SECTION

Annual Report for Calendar Year, 1960

The year 1960 continued to be an active period for the Publications and Reports Section, both in terms of regular and continuing public information and public education activities, and in terms of special projects.

The pamphlet National Institute of Mental Health (PHS Publication No. 20) was completely rewritten and reissued during 1960. This year also saw publication of a new health information leaflet on Alcoholism (PHS Publication No. 730), which has already had extremely wide distribution, and the 1960 edition of Mental Health Motion Pictures, A Selective Guide (PHS Publication No. 218). The film catalog is a completely new and up-to-date list of mental health motion pictures based on a survey of approximately 50 mental health education centers in 36 different States. A report of this survey was published in the May 1960 Service Supplement of the Educational Film Library Association. Highlights of Progress in Mental Health Research, 1959 (PHS Publication No. 736) was published early in 1960, and some 7,000 copies have been distributed to individuals and groups specially interested in mental health research, including subscribers to Mental Hospitals, a journal published by the American Psychiatric Association. Six of the special mental health Reference Guides were revised during 1960 and 12 press releases and announcements were issued. In addition, Careers in Mental Health (PHS Publication No. 223) and Facts on Mental Health and Mental Illness (PHS Publication No. 543) were revised and reissued during the year.

A new Public Affairs pamphlet Jobs and Futures in Mental Health Work (Public Affairs Pamphlet No. 296), prepared in cooperation with the National Institute of Mental Health, was issued in mid-April. Some 12,000 copies of this pamphlet were distributed to the members of the American Personnel and Guidance Association, accompanied by a letter signed by the head of that organization and by the director of NIMH. The pamphlet is addressed to high school seniors and college freshman and is part of a joint effort by the National Institute of Mental Health and the National Association for Mental Health to attract more young people to the field of mental health. P & R has also cooperated with NAMH on preparation and distribution of special materials for students and for counselors in connection with the NAMH's Mental Health Careers Program.

In addition to new materials, P & R continued to stock and distribute its wide selection of pamphlets, reprints, leaflets, brochures, and other educational and informational materials prepared by NIMH or by other sources. During the year, a total of approximately 200,000 pieces of literature were distributed. Over 1,600 Mental Health Week Kits (565 more than in 1959) were distributed to mental health associations, civic and service groups, and other voluntary organizations interested in promoting mental health activities. A great deal of literature was distributed in connection with professional meetings, at many of which NIMH exhibits were displayed.

During 1960, P & R prepared two new exhibits: (1) For Your Children's Mental Health, which summarizes NIMH activities in this area; (2) a table-top exhibit on mental health programming in the school. These two, plus five others, including one scientific exhibit on art therapy and one on studies conducted by the CNRC, were exhibited at 25 different professional meetings during 1960, including meetings of the American Psychological Association, American Psychiatric Association, National Education Association, American Public Health Association, American Orthopsychiatric Association, American Personnel and Guidance Association, Association of American School Administrators, National Conference on Social Welfare, and American Medical Association. A total of more than 50,000 people attended the meetings at which these exhibits were on display.

In connection with the 1960 White House Conference on Children and Youth, one P & R staff member attended as official delegate, another assisted in providing reportorial coverage, and a third served on the film committee for the Conference and was in charge of three separate film showings to the Conference delegates. P & R displayed a new exhibit on child mental health, and distributed a specially prepared pamphlet summarizing relevant NIMH activities.

P & R assisted the Community Services Branch in connection with publicity for the new police training film Booked for Safekeeping. Assistance was given the planning committee which is in charge of publishing the special monograph on the NIMH interdisciplinary study on aging. The special consultant on the P & R staff continued to provide assistance to State personnel in developing special reports on mental health programs, and prepared the summary report of the Second Carribean Conference on Mental Health. A P & R staff member served as interpreter for a considerable number of groups of French- and Spanish-speaking scientists who visited NIH during the year.

On March 22-24, 1960, P & R sponsored a meeting of State mental health information officers at the Woodner Hotel. This special meeting, planned and conducted by the Chief of P & R in cooperation with the Community Services Branch, was the culmination of 12 to 18 months of planning for improved communications among State mental health agency information personnel. Fifty-five representatives attended, of whom approximately 20 are full-time State mental health information officers; proceedings are being published. As a result of the meeting, information and public education materials are being exchanged by many of the States, and plans are being made to extend this activity to comprise a national clearinghouse of mental health information, educational and special report materials. Correspondence and contacts among State mental health information and health education personnel have increased considerably, and there has been new interest among State program people in developing or strengthening information programs. At the Woodner Conference, a steering committee was appointed to plan for increased public information and public education activity in State mental health programs; the Chief of P & R is a member of this group and has taken a leading role in its work. This group was responsible for planning and conducting a special session on

the public information needs of mental hospitals at the American Psychiatric Association's Mental Hospital Institute, held in Salt Lake City in October. It has been invited to conduct another program at next year's Mental Hospital Institute on the public information problems of the "open" mental hospital. In addition, because of the shortage of suitably trained personnel to carry on mental health information work, the steering committee is developing plans, in cooperation with a graduate school of communications, for special academic training in this field. The group is also devising plans for establishing traineeships and internships for mental health information personnel.

During the year, data on the information goals and activities of the NIMH were presented at special meetings of PHS health education staff, mental health consultants from the Regional Offices, and State and territorial health educators meeting with the BSS. A special report has been prepared which summarizes this material.

In addition to the above activities, P & R continued its routine and regular activities, including: (1) answering public inquiries (approximately 50 letters a week and many more times that number of telephone inquiries); (2) processing scientific, editorial, and policy clearance of over 400 professional papers prepared by NIMH staff members; (3) preparing special statements for the signature of the President, the Secretary, the Surgeon General, and the Director of NIMH; (4) preparing a considerable number of major speeches and addresses for the Director and other important officials; (5) preparing a wide variety of administrative and special reports, including reports in connection with budget appropriations hearings; (6) arranging special meetings and conferences for visitors, and arranging for lectures to be given by visitors; and (7) providing information on an extremely wide range of subjects to members of the press and to magazine writers, including free-lance and staff writers for such major magazines as Parents, Newsweek, Look, Harpers, Saturday Evening Post, and Good Housekeeping.

Annual Report* of the Basic Research Program, NIMH

January 1, to December 31, 1960

INTRODUCTION

This is my fourth and final Annual Report. Since each of the preceding reports undertook a discussion of general questions and since the questions themselves are interrelated, it may be helpful to introduce this last report by a résumé of the earlier discussions.

I

The first report, written in 1957, depicts the urgency for research which will enable men to understand how to substitute a just system of law for the present international anarchy. The most staggering problems facing man are no longer those of food, clothing, shelter, power and transportation, although these are not yet equably distributed; instead, the problems he knows least how to solve and which cause him the greatest tension are those relating to the perception of actions and of shibboleths, the translation of ideas, the momentum of traditional concepts, the adhesive behavior of groups, and the communication of ideals and goals. Men of all nations are in need, promptly, to possess vastly improved means for comprehending and coping with a myriad of problems relating to perception, memory and emotion. Men need urgently to learn how to become more constructively adaptive as interdependent individuals within a completely comprehensive, planetary level of social integration.

* As in previous Annual Reports, the Laboratory Chiefs have provided comprehensive statements of research progress achieved during the year. I am attempting here to continue an exploration of questions relating to broader horizons of the mental and neurological sciences. In the immediacy and seeming urgency of our daily existence, we tend to put these questions aside as if they were not prime to our purpose. Yet, I believe that they are truly pertinent to our ultimate best contributions to science and to our fellow man. These Annual Reports should be considered as fragments in a continuing insight-seeking discourse rather than as pretensions of discovered finality.

The several research domains relating to brain and behavior are the scientific disciplines most pertinent to the solution of problems that now seem so overwhelming. We need to know what are the limitations and what are the opportunities, how modifiable and how to modify man's capabilities to adapt himself to an environment wherein his greatest threat arises from other men. Man's aspirations for rational action, and, indeed, his definitions of what is rational, depend in large measure upon insights which can be gained only through an improved understanding of the fundamental processes of brain and behavior. Ignorance of both the limits and potentialities of this functional system acts as a handicap in present attempts to solve our most pressing social and political problems and leaves man's adaptive behavior almost exclusively subject to brutish pre-scientific impulse.

Defense and diplomacy cannot be primarily devoted to the advancement of concepts underlying interpersonal and social integration: they must proceed on the basis of whatever is the contemporary level of understanding of human relations, no matter how inadequate this may seem in the context of their problems. Defense and diplomacy are, nevertheless, providing a precious gap of time within which the essential political and social growth and adaptation must take place. It is what we accomplish during this gap of time by way of advancing knowledge and encouraging constructive social adaptation that will count most effectively. Progress in the discovery and communication of more rational ways to improve human relations will itself act as a relaxant to threatening tensions. Progress will be increasingly rapid as we deliberately cultivate the best opportunities for thoughtful and creative research enterprise in these fields. Our view is that the brain-behavior system is an evolutionary product which is playing its role in human development just as do teeth and claws: yet from this great transactional organ we can expect far more constructive and creative potentialities than from teeth and claws. The brain-behavior system, in our view, is a very incompletely exploited instrument for survival.

A further theme of the 1957 report discusses the essential role of creativity -- the sine qua non for conceptual progress in any field. No new level of understanding can be achieved without: i) a substantial mastery of the field of intended accomplishment, ii) an internal dedication and discipline devoted to a program of thought and action which has to surpass the contemporary limits of conception, iii) a capacity for nimble imaginative interplay of ideas and images, iv) a confident degree of intellectual nonconformity, and v) a capacity to communicate effectively the newly acquired conceptual formulations. It is obvious

that these criteria place special demands not only upon individuals who aspire to be scientifically creative, but also upon institutions which aspire to recruit and retain creative scientists.

II

The second in this series of Annual Reports, that for 1958, substantiates that all branches of science, and indeed all learning, depend in their ultimate formulations upon concepts relating to human sensory, mnemonic, judgmental and effectual mechanisms. Our present concepts relating to these transactional functions are not fixed and immutable but are changing rapidly. As insight is extended we shall be able to improve the operational definitions of reality relating to all branches of learning, those concerned with the rest of the universe as well as with ourselves. Our profoundest concern as scientists is with the intellectual content of our disciplines and with the creative processes essential to achieving substantial progress, as contrasted to fashionable satisfaction, throughout these fields. All administrative considerations ought to be devoted to the development, encouragement and exercise of these essentially intellectual faculties.

A further point of the 1958 report is that the idea of the separateness and incommensurability of mind and body is not an automatically selbstverständlich feature of human existence. Such a division is not presupposed by other thoughtful cultures. Our contemporary dualistic assumption was inherited directly from Greek scholars who first entertained the idea at a particular moment in history, around 400 B.C. No notion of the separateness of mind and body appears before that time. However, western civilization has embraced the idea for such a long time that it has become deeply imbedded in our language and habits of thought. We escape from the idea only by circumlocutions and we seldom really abandon it. I believe that this assumption is not only unnecessary but that it acts as an obstacle to our search for a more adequate understanding and to our efforts for the prevention and cure of mental and neurological disorders. This handicap is to be regretted for more reasons than simply because dualism fosters professional, intellectual and conceptual isolation among scientists who are trying to understand whole man.

III

The 1959 Annual Report concerns relations between science and society. Science as a human value, the place of science in the evolution of human values, the contribution of science in rationalizing and liberalizing society, the requirements in science that professional responsibility should pervade all scientific activity as well as the relations between science and society, the requirements for evaluating scientists and for evaluating science as a body of knowledge, and for making decisions which commit large proportions of society's wealth to scientific enterprise, the problems generated by the cultural interface between science and Government, and the administrative consequences of these considerations, are introduced for consideration.

The balance of the third report describes biological and social evolution as these proceed toward greater degrees of obligate cooperation and interdependence. Each step of this process is achieved at the expense of certain arbitrary modes of behavior which obtained at the lower levels of biological or social integration. But this loss is counterbalanced by substantial gains in freedom and power for self-determination enjoyed by the successively higher levels of organizational integration. The progressive enlargement of freedom within the more highly integrated systems can best be appreciated by scanning biological and social evolution over a longer time scale than is usually considered for the next essential step, that is, the establishment of a just and adaptive system for encouraging international interdependence. From these considerations follow certain implications relating to the comportment of the individual, family community, institution, nation and international organization in the attempt to provide a rational scheme for ultimate social integration on a planetary scale.

IV

In this final Annual Report my purpose is to examine some of the biological limitations and opportunities which underlie human capabilities for the social and cultural adaptations essential to survival. First, it is necessary to examine three problems which challenge us for our attention, understanding and solution.

THE CHALLENGES

" . . . we are here as on a darkling plain
Swept with confused alarms of struggle and flight,
Where ignorant armies clash by night."

Matthew Arnold

"War is the chief stupidity of man."

Charles Erskine Scott Wood

A. The Technological Challenge

In what significant ways has technology altered individual and national powers for action? In what ways does this automatically narrow the focus of responsibility for perceptions and judgments conditioning the utilization of national powers?

Within recent years it has become possible to pulverize the largest cities with only two or three packages of explosive. All other cities can be destroyed with a single package. There are many simple as well as sophisticated ways of delivering these packages. The number of packages available is said to be greater than the number of civic targets. Policies of threat and retaliation among the most powerful nations are roughly balanced, in an uneasy equilibrium, through the competitive development and deployment of instruments for massive extermination. For the first time mankind as a whole is vulnerable. The world is now a decade and a half deep into a gigantic arms race. History warns us that no previous arms race has ever ended peaceably.

Packages of modern explosive can be dispatched on the initiative of only a few men. They can be sent off from a variety of locations and delivered to any civilized target on the globe within minutes. Since surprise assault might blunt or disorganize counterattack, each antagonist is obliged to maintain himself in readiness for momentary massive retaliation. Within the last half century, the interval for all-out commitment relative to national security has shrunken from months to minutes. Any more deliberate judgment and widespread consultation must take place well in advance of the critical moment and be based on forecasted probabilities and contingencies which are impossible to anticipate completely.

Several non-atomic powers are busily preparing themselves for their own independent national capability for massive extermination. There will be several more members and members-by-alliance in the "nuclear club" within five years. Just what extremity of desperation in any given nation will trip off an international struggle involving massive extermination is nowhere publicly defined. In several countries, national purposes and national desperation are rather vaingloriously and personally defined. A large number of existing and potential triggers are capable of frustrating national purposes and of aggravating desperation. These triggers may suddenly reinforce one another in an uncontrollable "avalanche effect." These triggers are not under the confident control of any individual, any nation, or any existing combination of nations.

National constraints against the use of weapons for massive extermination may be moral or constitutional in character, based on fear of retaliation, and based on the realization that other possibly more successful ways to further national purposes may exist or may be developed. There are no enforceable constraints operating at the international level. Until constitutional machinery is adopted which will ensure an acceptable system for international justice, each nation is left to its own dreadful devices. Even if all of the present international crises were settled, other alternative and emergent problems would become equivalently critical. A quick riffle through any history book will illustrate that men face a continuing challenge of getting along with one another and sharing the world's resources.

Although men bemoan the cost of weapons for massive extermination, the cost itself does not provide notable constraint: weapons for massive extermination yield an order of magnitude less expensive destruction than any previous military techniques; it is only because the world is preparing the means for many orders of magnitude more destruction than was ever before contemplated that the costs seem extraordinarily high. If general destruction is man's principal object, he is now pursuing full tilt the most efficient and economical course to achieve that end.

Communication of threatening events and polarized national attitudes is instantaneous and world-wide. Unfortunately, it is commonplace now to suppose that charges and insults must be answered practically instantly and in the same vein; any other reaction is apt to be misconstrued both at home and abroad.

All of this has vastly changed the nature and potentialities of individuals and nations and is altering the whole fabric of human relations. It has placed the fate of all mankind and the disposal of all the monuments of human

achievement at the disposition of a few persons scattered around the world who have at their control practically unlimited powers for destructive action. The situation in which they find themselves and the national complexes they represent is dynamic and worsening. The individuals concerned are themselves committed in percepts, passions and judgments according to their own life experience which, of course, has largely been dedicated to a leadership role in their own idiosyncratic society. We have not yet comprehended much less reacted to the implications stemming from this technological revolution.

B. The Social Challenge

Unbelievable force has come into man's possession just as he has begun to find out that distortions deeply affecting perceptions, feelings and judgments are normally and inevitably incorporated as part of the baggage of all adults. World-wide communication has become practically instantaneous just as man has begun to appreciate the biological crudeness and inadequacy of the transactions of language. The world is becoming overcrowded just as man is beginning to appreciate the social value of an individual and to develop even a primitive insight into constructive human relations. Man has become proficient at polarizing mass attitudes of what is right and what is wrong, but is scarcely as far along in fundamental ethical reasoning (if, indeed, as far) as the ancient Greeks. There is as yet too little cognizance of the range of assumptions and criteria upon which any system of rectitude must be founded, and too little patience with the requirements for cross-cultural understanding on this score.

Man still faces the same two old choices if he would avoid war: either he must discover and establish institutions of government that will substitute a universality of values, purposes and means for the present conflicting systems, or he must provide institutions that will admit and protect differences of values, purposes and means, but still guarantee agreement in those actions essential to maintain order and at the same time accommodate change. As Walter Millis has declared of a world without war: "it would still be true, in the sense in which Jefferson presumably meant it, that 'the tree of liberty' would have to be 'watered by the blood of martyrs.' Men would still die for principle or passion; but they would not die as the helpless, systemic victims of a world order based upon highly organized and armed national sovereignties. Deprived of the easy simplicities and illusory securities of the war system, statesmanship would meet more, not less, difficult problems than those it must now confront; and it would take brains, illuminated by vision in the leaders and education in their followers to surmount them . . . A world from which

"organized war has been excluded would not be an easy one, and it would raise threats to various groups, economic interests, ideals and convictions which may well seem greater than the (still almost unimaginable) threat presented to all by a continuance of the war system itself. But it would be a viable world . . . its attainment, while immeasurably difficult, does not seem to be impossible."

But we have come only a little way in the required direction at the individual, national and international levels. For instance, the entire budget, from all member nations, for operation of the United Nations, the only organization having an internationally endorsed charter for arranging the settlement of international disputes, just equals the size of the budget for cleaning the streets in New York City. The cost of the United Nations, pro rated over the world population, is less than two cents annually. The yearly cost for armaments alone, not including espionage, propaganda and conventional diplomacy, pro rated in the same way, is more than two thousand five hundred times greater than this, and uses up nearly half of the total product of human and other resources.

1. The need for purposeful aspirations on a world scale. The most critical weakness of human society today is its lack of concerted purpose to achieve more comprehensive social and political integration. It is widely acknowledged that men of all nations are thrown together perforce of modern technology, but the consequences of this fact are not yet sufficiently taken into account in men's actions. It is as though we really believed that if we stood upon tradition, the present state of the world would revert to some more comfortable epoch in the past. Such a faith is folly.

Every human shares certain fundamental interests and objectives with all others: that it is better to be alive than dead, fed than starved, free than enslaved. There are other shared interests, but none is more fundamental and none is in greater present jeopardy as a result of international anarchy. Existing social systems are not arranged so as to safeguard even these rudimentary needs on a universal scale. It is rare for any existing system to advocate their fulfillment for anyone who does not belong to the same system. No individual can safeguard fulfillment of these needs for himself, nor for any other. No social system can safeguard them for its own people, nor for any other, although we continue to extend our faith on this possibility. The chief problem is to establish a new system that is sufficient to satisfy the needs for survival, sustenance and self-realization for all mankind. Of course, people will not then be satisfied, for even though alive, fed and free, they will still have problems enough; there will remain plenty of difficulties to challenge man's capacities for further social progress.

2. The need for purposeful actions on a world scale. The dimensions of social need and the arena of struggle for power and wealth are world-wide in scale. Perforce of these facts, creative thinking of ways to satisfy fundamental human needs and at the same time to arrange for the just settlement of disputes must be conducted on a global scale. Mankind has become so much one family that there is now no way to safeguard our lives or our welfare without achieving such safeguards for everyone. We need a fresh analysis of the role of all institutions bearing directly or indirectly on the requirement for a world government that supports universal maximum individual self-realization. Whether traditional ideas and traditional institutions can be helpful should not be presupposed prior to a thorough, objective and disinterested analysis of the requirement. What was adequate for less extended needs and aspirations will probably not now suffice. Parallel to this, we need research to enlarge man's grasp of the processes of human relations. Analysis, research and the required revision of institutions should be carried out with the deliberative participation of as many as possible of those concerned, that is, with the widest possible world base. This is essential in order to enable the consideration of this problem among the world's most creative thinkers, of which no single nation has a monopoly; moreover, world-wide participation will ensure maximal insight into the requirements and the means for modification of all pertinent institutions in the desired direction.

No nation or confederation of nations, acting unilaterally, can put world government into effect. They cannot accomplish this either by suasion or coercion because any unilateral endeavor would undoubtedly provoke a full scale war before it had gone very far. Thus, the only alternative to our present uneasy situation seems to be to invite the broadest world base of creative social thinkers to undertake research and deliberations leading to the development of plans for a more inclusive community of mankind. The research and discussions may not yield ideas upon which agreement can be established in the near future; but, if this objective is purposefully undertaken, sound and satisfying ideas will ultimately be elicited.

We have substantial reason to hope for progress in this enterprise through application of the methods of science. Social evolution in the past has come about through far slower and more haphazard processes. When research and discussion dedicated to this goal get underway, this fact by itself will tend to encourage the world leaders and mankind as a whole to be more tentative, to tolerate greater ambiguities and to exercise more patience concerning international relations. The findings of research and the results of world-based deliberations on implementation can later be submitted for national recognition or rejection and popular referenda to determine acceptability of any evolved plans.

The general situation will be improved by the encouragement and development of a world-view in all these objectives and undertakings; not a view to conquering the world but to making it safer and, in other basic ways, better for all mankind. Naturally, the attitudes and impulses which during the last four centuries have worked to create strong nation-states have established a prominent place in men's thinking and ways of life. Our United States' national experience of nearly two centuries and our individual strivings to improve national greatness, national security and national welfare are dominant features of our own existence. These attitudes and impulses should not be discarded in assuming a world-view. A world-view and world-government appear to be the only possible ways of securing enduring national greatness, national security and national welfare. Greatness, security and welfare cannot be sustained indefinitely on a merely national scale. As a nation, we are beginning to recognize this and to put it into increasing practice in our foreign and defense policies, foreign aid, military aid and mutual security programs. Something new has been added to nationalism, something which can accommodate continuing patriotic devotion to nationality. We are learning to be more rational about more complex and inclusive human transactions, to perceive the consequences of our actions in a wider context and longer view. Growth in freedom and opportunity for self-realization is known to increase with each more inclusive level of social integration and will increase even more when our identifications are extended to include all mankind.

3. Urgency of action. Most leaders in the powerful nations appear to comprehend that precipitation of all out war amounts to mutual murder and suicide: at present, a metastable military stalemate exists. This metastable stalemate, however, can be easily upset by desperate individuals and groups, even among the least powerful nations. They may conceive they have nothing to lose and perhaps something to gain, or they may simply behave irrationally. Therefore, time is a most precious commodity. We need to proceed in all deliberate haste toward the goal of world-wide social integration. What kind of time schedule might be estimated for this task? The necessary research and discussion need time; too urgent a desire to arrive quickly at an agreed upon plan may lead to inadequate improvisation and to the blunting of creative effort which might otherwise provide a far more desirable solution. The social and attitudinal changes required are probably equivalent in revolutionary dimensions to those which have taken place around the world during the last fifteen years: perhaps fifteen [illegible] minimum time if we begin immediately

4. The "idealistic" course is the only realistic course. Mankind can look back with justifiable pride on a number of now widely accepted revolutions in attitude and behavior which grew out of enlarged respect for human needs, human needs viewed increasingly objectively. We can expect traditional forms of thinking to reject and probably actively oppose research and discussion dedicated to the establishment of a system for the integration of mankind as a whole. Such pursuits may be thought of as "visionary," "idealistic" and "unrealistic." Yet, if any lesson can be clearly drawn from recent history, it is this: that many ideas labeled only recently as visionary, idealistic and unrealistic have already become the only tenable, practical and realistic ones. Much of the sinew and solvent of the most powerful nations have been consecrated in the process of learning that lesson.

Ideas, not things, rule mankind. Traditional ideas and consistent forms of behavior preserve continuity. They are reassuring to our immediate associates and bring us such comfort as attaches to the familiar. Yet, in the long run, this comfort may be illusory. For centuries, religious and racial tolerance were considered by all right-minded people to be contrary to any reasonable conception of morality. Epileptics and the insane were beaten and brutally incarcerated. The object of such treatment was to punish and drive out evil spirits possessing these individuals. All right-thinking people were convinced that this was in the best interests of both the victims and society. The use of lightning-rods was vehemently condemned as "an impious attempt to defeat the will of God" and as a means of "helping criminals to escape." Vaccination and even anesthesia were abhorred on moral grounds as contrary to nature.

It may bring us comfort that the only period of history we have to face is our own. Yet it remains to be seen whether we can meet the main requirement of our day, namely, to establish some kind of world order under a just system of law, within whatever gap of time we may have available. It is now high time that we assumed the obligation that our conscious awareness and our conscience thrust upon us. It remains to be seen whether we can individually and collectively generate the sense of confidence and purpose necessary to meet this social challenge. If we make our best effort and yet fail in this attempt, we cannot lose anything not already lost.

C. The Individual Challenge

1. The problem of individual commitment. A newborn babe can grow up to achieve a practically complete behavioral adaptation to any culture regardless of his ancestral background. Physiognomic differences scarcely interfere with this adaptation. A baby is readily accepted because he is commitable, yet uncommitted. Within a few years, however, a child's potentialities for adaptation to another culture become progressively limited. By the time he reaches manhood, indistinguishable behavioral adaptation is virtually impossible. Commitment involves internal polarization with respect to all aspects of life, likes and dislikes, even including things which are presumably detached from personal involvement. Physical terrain, the presence or absence, nearness or distance of mountains, flatlands, rivers, and the sea come to loom importantly along with personal associations in commitment and is notable in the commitment called "home-sickness."

Once the process of commitment has begun, in reference to language, customs and habitat, everything that is consistent with the initial pattern is easily and congenially adopted. Whatever is contrary to that pattern may be overlooked (not even sensed), may be sensed but dismissed as meaningless, may be met with surprise and incredulity, or it may be subjectively distorted and inappropriately acted upon, as if it conformed to the familiar pattern. The recognition of discordance with previous experience is characteristically associated with emotional excitement -- possibly anticipating the potentialities for threat and opportunity which accompany a novel experience. Actual adaptation to new patterns of language, customs and habitat is a slow and demanding process associated with many inappropriate responses.

Educational processes and the methods of science legitimize and encourage the systematic examination and objectification of percepts and ideas that may have only the most tenuous credentials. The foundations of intellectual growth depend upon this cultural legitimization. Education is properly called "the servant of all our purposes" (John W. Gardner). Education and discovery are both associated with intellectually satisfying response of "perspective dissolving surprise" (William Gorman). Gradually, unfamiliar patterns become accepted and ultimately incorporated into a new automatically functioning system of percepts, judgments and actions. Our capacity to perceive, to accept and to accommodate novelty slows down with advancing years -- as though we become increasingly impounded by our commitments. The important thing for us to comprehend is that the process of becoming committed is an indispensible and automatic part of our biological heritage, that it virtually ordains throughout all our processes of recognition and reaction

to all aspects of life, and that it is -- at least until late in life -- susceptible to amendment.

Our biological endowment thus equips us to adapt readily and to behave "successfully" in a given environment. The very factors which establish our easy and automatic behavior in our accustomed environment will operate to our disadvantage when we try dealing with a different environment. This is particularly true if we are incapable of recognizing the extent and significance of the novelty and deal with it as if it were familiar. Adaptation to experience carries with it a dominating expectation that the environment will be enduringly consistent. In a later section we will examine the extent to which all our sensations and ideas are dependent -- not upon the external events we are contemplating but upon the purposeful direction our lives have taken as a result of our individual idiosyncratic experience. The incorporated pattern does not give way easily to conversion, even when the necessity for a different adaptation is intellectually fully accepted and is reckoned to be worth one's life. For example, obeying the simple but contrary rule of turning your head to the right instead of to the left in order to avoid oncoming traffic turns out to be no trivial adjustment. Taken from the point of view of the need mankind now dimly discerns, to understand the percepts and judgments and to anticipate the actions of people from entirely different cultures, the problem of individual commitments can be seen to be interfering in a pervasive way with rational behavior.

2. The problem of conformity. Any kind of behavioral adaptation, any kind of individual or social progress requires nonconformity: nonconformity with one's own past adaptive, experience-guided behavior or nonconformity with the adaptive, experience-guided behavior of the group. The whole history of intellectual progress consists of steps taken which liberate us from purely reflexive behavior, from the limitations of immediate and imperious perception, judgment and response, from "common sense" and from traditional ideas. The "inertia" of men's minds is reflected in the intellectual turmoil which usually attends a shift from one level of understanding to the next: that the world is round, that the earth revolves around the sun, that blood flows through our vessels "as it were, in a circle," that men belong in biological continuity with the rest of the animal kingdom, and that something so inconsequentially small as germs can cause illness and death. Most of these intellectual conversions took tens to hundred of years. Each step, big or small, demands a break with the consistency of previous thought. Each contributor to intellectual progress must have been, by definition, a nonconformist. As Ben Shahn wrote, "Without nonconformity we would have had no Bill of Rights nor Magna Carta, no public education system, no nation upon this continent, no continent, no science at all, no

philosophy, and considerably fewer religions. All this is pretty obvious. But it seems to be less obvious that to create anything at all in any field, and especially anything of outstanding worth, requires nonconformity, or a want of satisfaction with things as they are. The creative person -- the nonconformist -- may be in profound disagreement with the present way of things, or he may simply wish to add his views, to render a personal account of matters . . .

"Yet, when it comes to the matter of just what kind of nonconformity shall be encouraged, liberality of view recedes. There seems to be no exact place where nonconformity can be fitted in: it must not be admitted into the university curriculum -- that would produce chaos. In politics it is certainly inadvisable -- at least for the time being. It cannot be practiced in journalism . . .In science -- least of all, alas!" Shahn goes on to conclude that "The degree of nonconformity present -- and tolerated -- in a society might be looked upon as a symptom of its state of health."

Saltatory advancement of social concepts -- the introduction of ways of thinking that change the entire character and direction of social progress, that lead to the acceptance of a substantially more fundamental ideal, that creatively reformulate the nature of a social problem or its solution, that cut short years of social strife -- are not likely to occur except where circumstances are especially favorable for nonconformist social thinking. The concept that "all men are created equal" was a product of such circumstances. Improvement in social theory, increase in the grasp of social problems and their solution depend upon advances of this sort -- essentially creative advances -- and upon their institutionalization. As Hastings Rashdall said: "Ideals become great historic forces by embodying themselves in institutions."

3. The power of purpose. It is not an accident that the words curiosity and cure come from the same origin. They imply being full of care, taking pains; having a desire to learn about, to comprehend; possessing empathy for and, thus, striving fully to understand the object of contemplation. Our guide for human progress, individually and collectively, grows out of our humane interests, understood objectively, in the long range and in the largest sense, humane interests made as consciously self-aware as possible. It is not likely that man can attain what he does not strive for. And it is impossible for him to seek what he conceives as unattainable. Thus far, human purpose has predominantly sought provincial advantage. This has been gradually enlarged from individual to family, to community, to nation, without there being unjust losses along the way. But the next step has not been seriously ventured.

By far the most important influence on social progress is consciously directed purpose. Men need to instill in themselves a sense of great purpose and high resolve to gain this most comprehensive level of social integration. The phrase "that all men are created equal" once played a role of the greatest importance in the establishment of our country. "That all men are created equal" became the reiterated definition of purpose of the Federal Government in the great campaign utterances of Abraham Lincoln. This phrase became Lincoln's principal personal and administrative theme and his main means for mobilizing what ultimately saved the Union. At that time, there was little the United States could do, nor was there so much at stake for the rest of mankind, regarding the global inclusiveness of that phrase. "That all men are created equal" has, to a regrettable degree, remained rhetorical even within our own borders since then. But there is every indication that the Founding Fathers took this principle seriously; they purposefully established institutions of government dedicated to its recognition and fulfillment. It is our turn now to support and improve those institutions and to extend the application of that phrase as widely as possible.

Education is "the servant of all our purposes," and so is science. Both seek the truth. They teach that the individual, community, nation and the universe is always in the process of becoming, and that none of this great transaction can be made to stand still. There is a certain anti-inertial effect on society contributed by education and scientific enterprise. Cultural integrity and the safeguards formerly dependent upon the preservation of traditional patterns of human relations can now be guaranteed through the broadening experience of education, combined with the creative contributions of science. Both debunk authority. They emphasize instead the intrinsically creative aspects of man's own life and his capacity to develop increasing degrees of freedom for himself and his fellow men.

Widespread acceptance of any new level of understanding in science is achieved through the examination of evidence that is made as free as possible from personal appeal, coercion, or "fashion" of thinking. Theoretical notions tested and found valid become stepping-stones in the pursuit of further knowledge. This progressiveness gives science much of its power. A further source of power comes from the scientists' attempt always to find simpler and more general relations to account for the vast schemes of nature. In this way neighboring disciplines come to dovetail and to reinforce one another. With emerging insight, such contributions become increasingly powerful and can be put into practice more quickly. The lead time between basic research and application is rapidly decreasing. In many fields, man's requirement for new knowledge is outstripping his capacity to exploit what is already known.

The social sciences have been relatively slow to develop, partly because the subject matter is vastly more complicated than anything that has been dealt with in biology or physics, and partly because there has always been a strong tabu against investigating social processes. The social sciences are now engaged in a transition from an empirical to a theoretically powerful corps of scientific disciplines. It is known by analogy from other branches of science that this kind of transition increases tremendously the scope and power of the enterprise. The capacity of these disciplines to provide insight and mechanisms for internalization of the controls for social behavior will ultimately dwarf the practical contributions of any other disciplines of science. The most impressive utilitarian value of science will attach to science when it becomes effective in the shaping of constructive human behavior. This contribution will have an equally important impact upon the mainstream of human intellectual activity, the philosophy of thought, vitality of ideas, and the generation of optimism as well as the opportunities for mankind.

Education and science are not automatically liberalizing. They can be encouraged to seek truths of differential value favoring one individual, one company or one nation. New knowledge can be deliberately fostered and exploited to yield powerfully disadvantageous consequences to other groups. In such efforts, education and science quickly outstrip any other contributions to unilateral advantage. But the same endeavor can be extended to seek truths of advantage to mankind as a whole. In this direction also, it is reasonable to anticipate that science and education will outperform any other mode of approach. Educators and scientists are professionally adaptive; they are certainly adaptive enough to make this transition; many of them already have. As a group, they are professionally dedicated to the discovery of larger and simpler patterns of transaction and organization. Furthermore, the community of teachers and scientists has been international in character since long before nationalism began to be a force in human affairs.

Mainly, it is to facilitate the establishment of worthier and more humane purposes that I urge the fostering of the broadest horizons in the labors of educators and scientists. Mankind has amply illustrated that it can always retreat to more primitive perceptions, judgments and actions. When research, encouraged in this way, adds new concepts to the traditional ones, men will at least have an enlarged freedom of choice and probably they will also enjoy greatly increased powers for constructive action. The rate at which meaningful new knowledge is appearing in the biological, sociological and psychological sciences, and the nature of the new information provide confidence that substantial progress can be made in the direction of helping all men grow more constructively adaptive as interdependent members

of interdependent groups. The question is not whether such achievements are feasible but whether they can be instituted within the time that may be available.

OBSERVATIONS RELATING TO THE NATURAL FOUNDATIONS FOR HUMAN ADAPTABILITY

What may be some of the bases for our commitment to early developed views of reality, patterns of ideation and judgment, and modes of behavior? How and to what extent may these interfere with re-adaptability? How compelling is previous experience in shaping and limiting what we perceive? How compelling is previous experience in our interpretation and reaction to novelty? To what extent do we remain blind to the unconscious influences of previous experience? What can be done in a positive way toward our gaining a more adequate insight into both the limits and opportunities of human adaptability?

In this section I shall attempt to be more explicit concerning the internal processes by means of which man adapts to a given environment and by means of which he must re-adapt to previously unexperienced patterns. For illustrations, I have selected a number of observations for brief outline: many of these are old and well substantiated research findings; some are drawn from commonplace experience; a few are new and must be admitted tentatively. To my knowledge, this particular combination of observations has not previously been assembled into one pretended ensemble. Nonetheless, the combination seems to form a coherent pattern. What is being sought for is a working conceptualization of man as an adaptive social being.

1. Developmental considerations. The presence of developing muscle cells in the body of the vertebrate embryo apparently induces the specialization and maturation of motor cells in brain stem and spinal cord. Motor nerves send connections to these muscle cells and begin transmitting impulses which induce muscular contractions before the sensory nerves have gained access to the periphery and before they have developed a capacity to transmit impulses. Therefore, at least in the first stages of life, responses to sensory stimulation are secondary, not primary, for action.

From the beginning, the embryo acts in an integrated fashion. Its first movements are mass actions. Later, more specialized and particularized actions arise through the individuation of motor patterns derived from the background of mass actions. As development progresses, mass actions are gradually held in check until, in the mature organism, they provide mainly the tonal and postural adjustments stabilizing the platform upon which an individuated act is carried out. During the process of generating new patterns of activity, the

nervous system continues to behave in an integrated fashion; newly integrated patterns are built up from older integrated patterns. The nervous system preserves a continuity of self-integrity during all adaptation.

Nerves serving particular muscles seem to develop a unique specification, an endowment received according to the particular peripheral relations they happen to establish. These are different specifications if deliberate transpositions are made in the peripheral motor organization. Something of the same sort seems to occur in relation to the central identification or specification of second and higher order sensory units, as we shall see later. These are perhaps the most elementary steps of commitment.

2. The origins of action. The nervous system used to be thought of as being activated primarily through the influx of outside stimuli. However, when direct observation of individual neuronal units became possible, it was discovered that some cells in each sense organ maintain a degree of "steady state" activity even in the absence of identifiable stimuli. Moreover, a substantial proportion of neurons in the brain and spinal cord show "spontaneous" activity from early embryonic stages onward, even during sleep, hibernation and deep anesthesia. "Spontaneous" activity and "steady state" activity are probably equivalent functionally; neither requires excitation from outside the neuron itself, although the rates of activity can be modified by outside influences. Spontaneously active units are found within all regions of the central nervous system, even in aggregates of neurons isolated from the rest of the nervous system. Various ganglionic masses throughout the brain interact with neighboring and even remote parts. The nervous system is made up of vast aggregates of neurons each of which exhibits its own activity, yet all of the aggregates are bound together into a mutually interdependent transactional system constituting an integrated whole.

It is evident that the nervous system is active as well as reactive. It is built for action. Even the earliest sensory messages enter upon a performance-oriented transaction. In respect to sensory messages, the central neurons govern: i) the degree to which any incoming signal can invade and alter the central transactional system, and ii) the degree to which such influence may be reflected during any subsequent motor performance. It is obvious that no sensory signal enters upon a tabula rasa.

For each unit in the combined total of incoming and outgoing neurons, there are at least five thousand central neurons whose activities are confined to the brain and spinal cord. The total number of these central neurons is estimated at a

staggering ten billion units. All of these elementary anatomical and physiological facts suggest that neuronal messages entering the central nervous system can come into direct and indirect relations with a very large number of mutually interdependent aggregations of neurons already organized into an integrated system.

3. Genetically determined and undetermined behavior. It is obvious that some sensory stimuli contribute quite directly to motor performance. Through genetically inscribed pathways, certain sensory signals can induce stereotyped reflex responses. Nonetheless, even these imperious reflex responses are clearly "conditioned" by ongoing activity in nearby and even remote parts of the central nervous system. This feature supplies the principal diagnostic value to the clinical testing for reflex responses.

Through more elaborate but still genetically ordained paths, the sensory system can play a "releasing" and guiding role in what has been referred to as "instinctual" behavior. Although reflex behavior is relatively fixed and is not profoundly changed by maturation and learning, instinctual behavior may await certain stages of nervous system or endocrine maturation and may be subject to some influence through experience and learning. Beyond reflexive and instinctual systems, however, all of the rest of the central nervous system seems to be far more modifiable.

It may be concluded that reflex pathways are the least modifiable, most direct, and shortest-circuited; that paths relating to instinctual behavior are longer-circuited and more modifiable; and that the remainder of the central organization is relatively long-circuited and undetermined. This most modifiable compartment does not seem to be genetically precommitted to specific sensory or motor patterns but is more or less available for any commitment. This potential for commitment is far more flexible than that relating to the commitment of sensory and motor units alluded to in the section on embryonal development.

Our problem relates chiefly to this longest-circuited, most modifiable compartment: What evidence is there that this system is not committed at birth? What evidence is there that this system can be committed to neuronal patterns relating to experience and that, following such commitment, the system is relatively less free for re-commitment?

It is reasonable to suppose that because of the vast numbers of neurons involved and because of the tenuousness of many of the mutually interdependent relations, extremely subtle changes in time and tide of activity in only a few units

can have enormous effects on the outcome of any given initial state. But it is important to remember that such a system can only progress from one stage to the next, from an uncommitted but integrated performance to a committed and still integrated performance. In each successive state, the organism is active and acting, even if the action is simply to hold more overt action in abeyance. The organism can never revert to its original uncommitted state but must instead progress from one committed state to the next and so on. Presumably this progression will be retarded according to whatever in the next pattern of adaptation may be incongruous or conflicting with the ongoing integrated system.

Pertinent to these organismic considerations is Whitehead's solution of the apparent conflict between concepts of permanence and becoming, and between determinism and free will. The organism becomes something else on the basis of its given ("permanent") endowment; direction of "free will" is based upon what has been determined up to the present: direction is always from somewhere, from something.

4. The processes of neuronal commitment. (a) Congenital absence of sense. Persons born totally blind never know what vision is like. They have no visual memories or visual dreams. They do not "see stars" or anything else "visual" if bumped on the head. Individuals who become blind after having some experience with sight, that is, after the first few years of childhood, usually retain for the rest of their lives powerful memories of visual patterns. They may have vivid impressions of color and light elicitable by memory or dreaming. Kimio Eto, one of the best koto players in Japan, describes his visual experiences as follows: "I was very fortunate; when I went blind, I was old enough to know color quite vividly. As I play, certain notes and melodies bring back certain colors, in a perfect form. Somehow, I feel that my world must be one of the most beautiful."

Persons with congenital cataracts who can see only diffused light during childhood do not have good vision immediately after the cataracts have been removed, even if they have satisfactory corrective lenses. It takes such individuals a long time to learn to employ visual signals independently of their other sense modalities in the identification of simple geometrical figures. It takes them even longer to develop any confidence of action in circumstances of visual dependence. It is doubtful whether they ever do see "normally" if the cataract removal has been delayed beyond childhood. (A roughly parallel account is given of chimpanzees raised in complete darkness for some months. The animal studies counter some of the ambiguities obtaining in patients with congenital cataracts, e.g., that there might have been other congenital defects affecting vision, or interference by virtue of the surgery or post-operatively inadequate optical accommodation.)

We are led by these facts to surmise: i) in the absence of access to the outside world through a particular sensory modality, the otherwise appropriate brain pathways do not organize central representation of that aspect of the world, ii) sensory experiences in early childhood may be lastingly committing with respect to central representation, and iii) the absence of such childhood experiences may be limiting with respect to the ultimate fittness of that central representation.

(b) Phantom sensation. When a limb is congenitally missing or is amputated at birth or shortly thereafter, there is no evidence of phantom sensation referable to the missing part. Nevertheless, when a limb is amputated anytime after early childhood, the individual concerned uniformly has a phantom which usually persists for the duration of his life. Phantoms may be associated with the loss of fingers, toes, penis, breasts, ears or nose, but the most vivid and enduring phantoms follow major limb amputations. Conscious awareness of phantom parts relate to those to which conscious attention is ordinarily directed; thus, the phantom fingers, hand, wrist and elbow may be vividly experienced, whereas the forearm and upper arm may be foreshortened and only vaguely experienced. The phantom can usually be described in detail as to its exact position in space and in relation to the rest of the subject's body, its motility, and its participation in "voluntary" movements. There may be detailed sensations relating to temperature sense, muscle tension, joint position, nail bed, skin tension, tickle, whether hairs are erected or not, etc. Normally, phantoms can be caused to change position, to "move at the free will" of the subject. The subjective feeling of "thumbing your nose" with a phantom is said to be exactly equivalent to that of the normal extremity, just as easy but not so risky.

We are led further to surmise: i) the specification of "sign" given to second and higher order sensory units by virtue of sensory experience is integrated into patterns, ii) these patterns involve sensory and motor and sensori-motor integration, iii) these central patterns continue to remain coordinated even in the absence of the peripheral organ (the limb) and the peripheral motor nerve endings and effectors and the sensory end-organs which are nominally conceived as responsible for the origination and organization of peripheral sensation. Formerly peripherally assigned functions have been taken over, as it were, by second and higher order motor and sensory neurons which continue to function in harmony in accordance with their special commitments through actual experience. This presumably means that muscle, tendon and skin receptors activated in concert during the experiences of active and passive movements of the previously intact limb have somehow conferred "pattern integrity" as well as "sign" upon higher order sensory and motor units relating to that limb. This "pattern integrity" and "sign"

never appear without abundant explicit personal experiences. Yet commitment of childhood is adequate for an indefinite duration of the phantom, even in the absence of any further reinforcement from the missing extremity. Despite intellectual and visual evidence to the contrary, the phantom continues to survive in conscious awareness and the previously experienced integrated patterns remain inscribed and integrated in their commitment.

It might be interjected that the phantom represents nothing more than "memory," but this begs the question: Where does this "memory" reside? The phantom (or "memory") can be modified by cooling the amputation stump, by injecting the amputated nerve trunks and the local spinal sympathetic ganglia with procaine, and, in the case of a lower limb, by spinal anesthesia. Furthermore, phantoms following transection of the spinal cord are specifically and characteristically different from phantoms following limb amputation. These facts combined to suggest that the phantom as a "memory" not only originates from ascending impulses but may continue thereafter to have its "roots" in parts close to the original input stages.

(c) Conditioning, learning, and the process of becoming. The natural history of developing perceptual, motor, cognitive and social skills is being learned through observations in various branches of psychology, anthropology and sociology. Considerable is now known about conditioning and other forms of learning, including social imitation, and learning dependent on the symbolic processes of language and mathematics. Learning in any form appears to depend upon: i) confrontation of the subject by an unfamiliar configuration, ii) devotion by the subject of attention to that configuration, iii) existence in the subject of some degree of motivation or drive, iv) development of a new central neuronal configuration yielding ideas or action relating to the unfamiliar configuration, and v) feedback to the subject of information respecting success or failure, appropriateness or inappropriateness, of his ideas or actions as related to the unfamiliar configuration. Failure of any one of these five essentials precludes learning anything at all.

It is also obvious that the subject must make use of an internalized neuronal scheme of the universe in which he and his body parts are represented in organized ways which can be variously articulated with systems representing objects other than himself and with systems representing time and space. Very little of this arrangement appears to be genetically determined, as we have observed. History teaches us that men have held very different notions about themselves and about objects around them; certainly, in the natural history of the individual, such a linked succession of different concepts of self and beyond self takes place.

Early psychological studies emphasized the high degree of presumptive correspondence between physical objects and the subjective report of these objects as perceived, and the high degree of correspondence among reports from different individuals observing the same object. This tended to stress the impartiality and consistency of the perceived world. Naturally, the first test objects were selected as being relatively unambiguous. Naturally, the subjects were required to "pay attention" to the object and were given certain other stabilizing instructions. The subjects were advertently and inadvertently highly motivated to provide what might be considered "normal" subjective reactions. It was quickly recognized that "inattentiveness" or "fatigue" have remarkable effects upon thresholds and other characteristics attributable to the relationship between object and subject which characteristics, under stricter conditions, may be quite stable and predictable.

Certain objects turned out to be interpreted as having "size constancy" and other attributes which depend upon the subject making certain sophisticated assumptions concerning both space and object, both of which acts of assumption are based on previous and not on the experimentally obtaining experiential conditions. Later it became fashionable deliberately to influence perception by inducing in subjects certain prescribed expectations. Both past experiences and induced expectations are profoundly influential on percepts, judgments, and behavior. Still more recently, it was demonstrated that an individual may be converted in his perception or judgment of even simple and familiar geometrical configurations by confronting him with contrary ("incorrect") but concerted views of other subjects. The interesting thing is that, under such conditions, objects come to appear to the subject as if they actually do correspond to the socially adopted view. Other investigators pointed out that children are more reliable witnesses than adults for certain kinds of objective reality. This is assumed to be because children lack the persuasive commitments built into the adult as a result of his experience.

From infancy, through puberty, adulthood, "parentage" and finally old age, we are really a succession of different persons. We have different appetites, perceptions, emotions, activities and different capacities for conscious awareness and responsible behavior. At different ages, we obviously have different shemes for ourselves and for the rest of the universe. Not only do we change rapidly, but the world changes rapidly around us. We tend to adjust ourselves to these changes through a combination of adapting ourselves to circumstances and adapting circumstances to our changing needs. In the process, we tend to underestimate the true extent of the alteration of our internal and external state. For instance, as adults, we would have a difficult time converting our body image back to a pre-puberty

stage even though we have had abundant experience with that former personal body scheme. We have since that period become something else. We are continuously in the process of becoming.

On a shorter time scale we are continually changing in ways that profoundly affect our perceptions, judgments and actions. For instance, when we are satiated, it is difficult for us to feel an adequate compassion and urgency for those who are hungry. For this reason, a good restaurant does not permit cooks and waiters to eat until after serving the customers. When we are food deprived for 24 hours or more, our attention is swiftly attracted and held by food odors, our judgment is biased respecting the value of, say, an onion, and our actions are both consciously and unconsciously dedicated to food procurement. Although such tides of appetite and satiety are generally short run, if a man is chronically starved or cold or penurious, he learns to take advantage of features of his environment not attended to by others and he may develop a life-long commitment relating to specialized perceptions, judgments and actions.

The educational, social, political, military and economic changes which have revolutionized the pattern of lives within this generation are eloquent testimony to change and to the range of human capabilities for adaptation to change. We can appreciate from the experience gained in these years the powerful influence of conscious and rational dedication to successful adaptation. We can likewise appreciate the stimulating as well as disruptive potentialities imposed by change. Yet, characteristically, we do not project into our views of the future a degree and rate of change equivalent to what we have gone through in the past. This limitation of projective imagination tends to influence us to underestimate our powers for conscious dedication and rational election to the direction of successful accommodation among the various alternatives we are confronting.

(d) Sensory deprivation. When normal subjects are placed in circumstances of sensory deprivation (really, a reduction or monotony of sensory input instead of true deprivation), they characteristically develop certain sensory, judgmental and motor defects. This is true whether the deprivation is induced by confinement in a light-proof, sound-proof cubicle or submergence in a constant temperature pool of water. After some hours or at most two or three days of confinement, subjects begin to lose their normal ability to control their thought processes. They cannot sustain a line of thinking or bring to mind familiar ideas. Soon thereafter hallucinations may appear, beginning with visualized geometrical patterns and going on to include auditory and somesthetic impressions. Hallucinations thereafter become more elaborate and intrusive, and eventually may involve elaborate perceptions of bodily movement, voices and moving scenes. The subject's ability to respond to his own or to outside commands, to discriminate test objects, to think

in concrete or abstract terms, and even to perform correctly simple motor skills such as handwriting and walking, becomes disturbed. Recovery may take several hours or even days.

One is left with an impression from such studies that contact with "reality" may be more dependent upon experience than we generally suppose. We presumably are normally encountering frequent and automatic validations and cross-validations of our internal circuits through continually varying perceptual, judgmental and action experiences. This process may be contributing to the maintenance of "normalcy." When this process is substantially reduced as in sensory deprivation, "spontaneous" patterns of activity in the central nervous system may begin to exhibit their independence from the controls derived from continuing perceptual, judgmental and behavioral experience. Such experiments have suggestive implications as to the nature of hallucinations experienced by lonely explorers, prisoners, truck drivers on long and monotonous runs, febrile and isolated patients, phantom sensation, and perhaps also frank mental disorder.

Pure-bred Scotty dog litter-mate puppies have been separated so that half of them could be raised in an experience-limiting environment and the other half in private homes. The experience-limited animals developed over a period of months a persisting hyperactivity and an incapacity to learn simple discriminations and motor performances which were quickly comprehended by their siblings. The effects of upbringing in such severely limiting circumstances appear to be long lasting.

We are led to conclude that the relationship between experience and internal neuronal processes relating to perception, ideation and action is one of great interdependence. Varied experience may be indispensible in fostering and assuring continuity of a capacity to maintain contact with and to deal appropriately with the changing world.

(e) Sensory stimulation. It is a commonplace experience to alight from long, noisy airplane flight and thereafter for some hours to experience a continuing "noise in the head." Similarly, hair blowing on scalp or forearms for some hours may be followed by persisting sensations imitative of the "blowing hair" experience. Disembarking from a rough ocean crossing may be followed by continuing or recurrent sensations of motion of the now stable environment, as if it were a moving ship at sea. The percept may be associated with a wide-based and "rollicking" gait said to characterize the sailor ashore. The French refer to this illusion of motion as mal de débarquement. If the seas have become gradually rougher during the crossing, the first occasion for vomiting from sea sickness may be experienced on solid land.

One is led to interpret this as a phenomenon of temporar functional commitment. It underlines the reality of ongoing central activity as a controlling force in perceptions and actions, and illustrates once more an experience-imposed lack of correspondence between percept and outside reality.

(f) Related internal processes. Recently developed techniques have been introduced which make possible crude observations in experimental animals of internal changes accompanying adaptive behavior. Only the most primitive and preliminary insights have been gained thus far, but the domain is vast and promising. A little is now known which can provide internal (neuronal) linkage patterns complementary to the external (behavioral) linkage patterns established by the social sciences. Obviously the nervous system provides whatever mechanisms we have not only for physiological coordination within the individual but also for his comportment in the physical universe and his management of human relations as well.

It is now possible to delineate certain generalized changes of functional activity within the brain which are associated with alterations between sleep and wakefulness. The mechanisms of "arousal" and "attention" and the more particularized "orienting reflex" are understood in a preliminary way. Activation of certain brain loci induces animals to behave as if they were being "rewarded"; activation of other regions has a "punishing" effect; activation of still other parts of the brain is neutral with respect to such reinforcements. Some parts of the brain are clearly associated with appetite and other parts, physiologically linked with these appetitive centers, are clearly related to emotion. Both the appetitive and emotion systems seem to be bound up in what we mean by the terms "motivation" and "drive." A wide variety of conditioning experiments has revealed some degree of modifiability of at least certain of these central circuits. Central responses to standard sensory signals, for example, are notably different depending on whether or not the test stimuli are associated with other "significant" (rewarding or punishing) stimuli.

5. Effects of commitment. This section is based largely upon experiments conducted by the late Adelbert Ames, Jr. Although his work does not yet have a widespread influence in contemporary thought, this is undoubtedly relateable to the difficulty imposed upon the communication of insight into transactional mechanisms by means of a language built for expressing linear cause and effect relationships. Ames resorted primarily to demonstrations to convey the meaning of his work. Ames's demonstrations, unfortunately, take quite as deliberate and conscientious study as do scientific papers. They are frequently mistakenly treated as if they were simple tricks or displays and probably no more sophisticated than vulgar parlor magic. Nonetheless, the hypotheses and interpretations which were the reason for Ames's development of

these demonstrations are among the most profound and far-reaching ideas concerning man's relations with the universe around him and presumptively with his fellow man. John Dewey wrote that Ames's work "is by far the most important work done in the psychological-philosophical field during this century -- I am tempted to say the only really important work."

Ames's experiments deal with the perception of distance, objects and motion and of the sequential significances of objects in motion in relation to the observer and his capacity to anticipate the future course of such objects. He first demonstrates that the content of perceptual awareness includes striking contributions on the part of the observer. Such contributions are not obtainable from the objective reality of the present, but are based upon assumed familiarities which, in turn, depend upon the observer's experience with cues now recurrent in the present situation. Physiological events as well as object-originated cues are compounded in our perceptual awareness. Ames sought demonstrations of what we "subjectively" contribute to our perceptions of "something out there." Our past experiences contribute weighted information on what we have most usually experienced at times when we had similar sensory cues. Brightness, size, parallax, convergence and disparity are visual cues which contribute to assumptions about location and movement of objects. Characteristics such as hardness, malleability, resiliency, combustibility, etc. are assumed on the basis of more or less similar visual, auditory and somesthetic cues.

"We cannot reach an understanding of what the environmental situation does contribute to visual awareness if we think of the environment as an immediate, instantaneous existence independently apart from environmental situations earlier experienced by the observer or independent of environmental situations we might experience later." In encountering non-correspondence between what we assume to be the reality of a given situation and our prediction of its consequences, we feel insecure as a function of the intensity of the discrepancy of cues. "Fundamentally, our feelings of security or insecurity as to subjective significances arise from processes below the level of awareness... These sensed feelings may be the original value judgments."

Ames's demonstrations show that we make instantaneous and complex adjustments to perceived cues in the direction of assuring correspondence between previous experiences and the present conscious awareness. For example, if you put on aniseikonic glasses and observe the room in which you are now sitting, you will instantaneously and automatically correct for the distortion imposed by the lenses in such a way as to maintain your percept of the room according to your previous experience with architectual symmetry. Through use of

different lenses, different problems can be imposed upon your capacities to make the present percept conform to your previous experience. One pair of lenses, for example, can project on your retinae cues which correspond to the area of the ceiling being twice that of the floor, the walls sloping out with appropriate changes in the angles relating walls to each other and to the floor and ceiling. Other lenses can be made to cause a 30° slope of the entire room. Nevertheless, almost all adults fail to see anything discrepant about their percept of the room which is given "normal" room configurations. You may feel only some unsureness about this complexly readjusted percept. Only after some experience with aniseikonic glasses it is likely that you will be able to perceive the room as distorted according to the veridical visual cues actually being presented to your sense receptors. The basis for instantaneous and automatic adjustments of incoming cues to fit your past experience lies with you, the observer, and not with the cues. A beginning schoolchild having less experiential commitment with the usual architectual symmetry of rooms will far more quickly perceive the distortion. An adult savage presumably would similarly quickly perceive the room as distorted.

If aniseikonic glasses which will cause an apparent tilt to the environment are employed out-of-doors, the tilt is readily recognized in looking at fields and rolling hills. But, if the scene contains a lake the tilt is automatically rejected in conscious awareness presumably because sloping water violates previous experience. If, instead of using aniseikonic lenses, a room is actually distorted, you will perceive the room as normally symmetrical. But now individuals in the room are perceived as distorted in size according to the perceptual accommodations imposed by assumptions about symmetry of the room.

Expectations as to future consequences ("sequential significances") have their impact on actions. If you are asked to bounce a rubber ball, a steel ball, or a golf ball, you will make appropriately different movements in order to catch the ball off the bounce. These movements are based upon previous experience with similar objects. If a ball of putty is substituted, you will not expect it to bounce. But if the ball of putty is made of a silicone compound known as "silly putty," malleable as it is, it will bounce much more briskly even than a rubber ball. In order to perceive the nature of objective reality and to predict its "sequential significance" and the influence of your actions on the succeeding sequence of events, it is necessary to make a host of assumptions and predictions. The skill of an accomplished athlete depends on his ability to make accurately weighted assumptions on the basis of his extensive past experience, weighted especially according to experiences most closely resembling the present.

Demonstrations and experiments of this kind indicate that an observer develops a conscious awareness only of those aspects of his surroundings which "carry significances" to him. These significances sustain, extend or vary the satisfaction of his purposes as these are carried out in action. "An observer's experiences have compounded into a 'subconscious' recognition that the significance of his environment is not disclosed by his perception of what and where 'objects' are but by the consequences of his purposeful behavior guided by his prehensions that he knows his perceptions of objects are only symbolic referents. ... Learning occurs only in relation to events of which the learner has already had experience and only under conditions of non-correspondence between his prehension of sequential events and the sequences occurring." In other words, we admit to conscious awareness that which has meaning to us in relation to our purposes. We learn from those things admitted to conscious awareness which do not correspond to our basic assumptions. Overcoming a non-correspondence by inappropriate construction of assumptions does not eventuate in learning new characteristics of the environment but in a lost opportunity for learning and a subsidence of the internally generated urge to establish correspondence.

Ames showed that objective reality, the neuronal equipment required for its prehension and the conscious awareness of the perceived object constitute a dynamic triad. Perception is not selbstverständlich. Thus, the discrepancy between a philosophical solopsism on the one hand and materialism on the other, which discrepancy was discussed from another point of view in our 1958 Annual Report, is solved by Ames by saying that perception is either "both or neither." "In a word, past perception, past surroundings and past physiology are now acting on one another. This is why the content of perception is not self-explaining. To content you must add intent. The content is prognostic and directs your behavior as purposeful actions. Purpose figures in perception, and perception is propulsive, future-directed and future-perceiving . . . Correspondence [between sequential events as forecast and sequential events as evolved] matters only in relation to purposes. This is why the shooting, which the perception of a deer starts off, must be aimed at a corresponding deer and not a non-corresponding man. Seeing a deer and hitting a man defeats your aim. So, when you are driving, does your anticipation that an oncoming car is going to stop when it just doesn't stop. Perceiving an ongoing event and prehending its future consequences are the primary gradients of our keeping ourselves alive and diversely growing."

In human relations, we must perceive and predict transactions among individuals who are perceiving the world

and each other according to their own previous experiences and giving weighted assumptions of these past experiences as controlling influences in the forecasting of their own and others' behavior. Much as we may wish to make a perfect forecast of other persons' behavior, we discover it does not have such reliability. "Customs, mores, rights, rules, statistics are prescriptions for the repetition of behaviors. We are not born with them; we are taught them. . . Most of education consists in passing them on from one generation to the next. Most of legislation consists in ordaining and improving similar coercive repetitions; some commanding, some forbidding behaviors. . . That the prohibitions are but moderately enforceable and enforced, indicates the spontaneity of variation and the ineluctable pressure in each living individual of the propensity to dissent. The judiciary functions as an arbiter between the claims of collective repetition and individual spontaneity. This is why it serves not justice but the 'public policy,' which may on one occasion see conformation as advantageous, on the other, look to variation. . . Apparently, we think of the motivational patterns in others by means of those in ourselves; and no matter how large the correspondence between them, there is an area of non-correspondence whose depth and breadth make an abyss of misprehension. . . Apparently very few of us know enough about human nature and behavior to recognize that the trouble is usually due to our own misprehension of the consequences of sequential events we initiate. And this misprehension of the consequences of the effect of our behavior on other people is due primarily to our failure to take into account the 'form worlds,' purposes and aspirations which others have in order to protect and further their own well-being and development."

6. Conversion of commitments. About the turn of the century, G. M. Stratton, in a series of brilliant experiments, demonstrated that it is possible to induce rather complete conversions and reversals of committed patterns. Stratton's experiments have been widely replicated and extended since then but their mysteries are by no means plumbed. In brief, by means of lenses, it is possible to project on the retina an inversion of the visual field, or a reversal of left and right sides of the field, or a combination of both up-down and left-right reversals in the same pair of glasses. When you first wear such glasses there is considerable uneasiness and conflict, but after a matter of days of continuing experience, "correspondence" is restored! An individual can thereafter ride a bicycle, fence, play golf and perform other sports with ease and skill.

In the process of getting used to an upside-down world, you begin by making elaborate conscious thoughts concerning

the course and improvement of movements: you "know intellectually" that it is necessary to move your hand downward in order to reach a nearby object which your conscious awareness labels as above your line of vision, but your previous commitments dictate otherwise. Making the movement in the right direction requires at first deliberation; many inappropriate actions take place. Later, entirely appropriate movements are made smoothly and automatically. Still later, and after a further period of experience, you discover that there is no further conflict of cues: the perceived world is restored to its traditional right-side-upness. Learning to adjust to a left-right reversal is more difficult, requiring severalfold longer experience. Learning to adjust to the combined up-down and left-right reversals is yet more difficult.

In these experiments all identifications of the outside world attaching to "thereness" have to be specifically relearned in all visual patterns despite the non-correspondence of this requirement with past visual, somesthetic and motor experiences. When the glasses are removed a similar (but distinctly shorter) period of adjustment is required. That is, soon after the glasses are removed, you cannot perform simple acts like riding a bicycle because of the new "non-correspondences" between incoming cues and the assumptions built up during recent experiences wearing the reversing lenses. The world briefly appears "upside-down" once more.

The general principle involved here has been extended with roughly analogous results in relation to motion and color as well as form cues in vision, auditory localization reversals, transplantation of tendons and muscles, etc. Apparently man's nervous system can accommodate certain kinds of conversion of certain long standing and elaborately inscribed commitments. This is not possible for the salamander, however. Visual field reversals in the salamander are inappropriately responded to in an enduring fashion. Presumably, somewhere between lower and higher vertebrates a certain degree of freedom for functional reorganization has been achieved.

7. Interpretive formulations relating to these observations. In this section we intend being deliberately speculative. To some extent we are discussing "a bag of cats and dogs." Nevertheless, the following tentative suppositions commend themselves for consideration:

(a) Not much of the nervous system is indubitably and inevitably committed in the beginning, not even the motor cells of the "final common path." If the motor and sensory units become the most firmly committed by virtue of the particular attachments they assume, the second and higher order units associated with them are less imperiously committed.

Even the circuits devoted to instinctual behavior are subject to influence by experience. It may be supposed that neuronal mechanisms still more distantly articulated with the direct input and output systems may be still more susceptible to modification according to experience.

(b) The commitment of motor and sensory units seems to be quite firmly established early in life. The commitment of second and higher order sensory and motor units in relation to the body image appears to take place on the basis of the "sign" committed to particular muscles and sensory end-organs and also on the basis of the "pattern integrity" built up through coordinated sensory and motor experiences and co-ordinated experiences in which sensori-motor patterns change in a combined and integrated harmony. Body image formation apparently occurs sometimes in childhood and may last a lifetime.

(c) Other kinds of commitment may take place in a more plastic, alterable form. The neuronal circuitry of this latter variety is still mostly a mystery and calls for more penetrating analysis. Apparently it is an endowment of higher evolutionary forms. Somehow experiences in perception, judgment and action are laid down in unconsciously operating patterns which contribute in a continuing way to conscious awareness and behavior. Past experiences are weighted according to the familiarity of apparent recurrences in the present and are closely bound up with aims and purposes. It is impossible to disentangle which parts of any ongoing experience are based strictly on "objective reality" and how much of our present conscious awareness is contributed from the dynamic composed of our previous experiences and our purposes. As Ames has established, we cannot be aware of the relative proportions of the working triad: outside object, conceptual content, and human purposes, excepting through painstaking experimental isolation of the three interdependent components. This is the main business of science. But the pragmatic solution of "what works" and the universality of experience, which are so useful in most other areas of science and technology, are difficult to apply to human relations because of the requirement to obtain a full consciousness and consideration of the attendant assumptions which in turn relate to idiosyncratic individual and cultural experiences. The homogeneity of the "stuff" of contemplation of the physical sciences is wanting here.

(d) Internal processes of commitment occlude from our perception those things which are lacking in significance for us. This makes it difficult to perceive changes in our environment excepting in accordance with the extent of whatever familiarities attach to an otherwise novel situation; novel aspects of the environment need to be painstakingly apprehended, through familiarizing experience with the non-correspondences

obtaining between our assumptions and forecasting on the one hand and what later happens. Learning depends entirely on our facing up to the non-correspondences between our environment and our upbringing to that moment. Failure to reckon with non-correspondences precludes our learning anything or achieving diversified growth or departing from the dead center of our present existence. Failure to deal with non-correspondences limits our knowledge of the characteristics of nature and reduces our potential predictive capabilities upon which survival and well-being depend.

(e) Internal processes tend automatically to dispose of non-correspondences through a process of internal misprehension of the non-familiar. It is as though the nervous system, having to work upon learning, lazily precludes acceptance of non-correspondences for as long as it can -- that is, until failure of behavioral achievements, assignable to failure to find a mechanism for correspondence, enlarges our purposes to correct that defect. Misprehension results in an instantaneous and comprehensive oversight or misinterpretation of all of the incongruent, non-corresponding cues. This failure is likely to occur whenever the incoming incongruent cues are weak or are overshadowed by familiar corresponding cues. It is especially likely to occur in a social context among persons having essentially the same background of experiences. There is a powerful tendency toward conformity in perceptions, judgments and actions resulting from the socially integrating purposes of being considered a "normal" being and of considering oneself a "normal" being among our fellow men. This tendency for social conformity powerfully reinforces our internal experience-endowed assumptions and forecasts.

(f) It is not only difficult to perceive non-correspondences, but learning is centrally dependent upon our recognition of such non-correspondences (consciously or unconsciously) within a framework of purposive desire for survival and growth.

(g) It is evident that we are not only continually weighting assumptions according to experiences but we evidently depend upon a continuing processing of sensory messages in order to maintain functional control over the relations between outside stimuli and our conscious awareness. Thus, sensory deprivation is followed by a relaxation of correspondance between "objective reality" and conscious awareness and, also, by a relaxation of internal controls by which we can direct conscious awareness.

(h) To continue in the process of becoming, to increase our comprehension of the [illegible] of ourselves and the universe around us including our fellow men, to learn, to create and to achieve anything new requires: i) exposure to conditions leading to a non-correspondence between our projections based on past experiences and evolving events, ii)

recognition by us of the non-correspondence (this implies that significance is attached to the non-correspondence with respect to our purposes), iii) devotion of attention to those characteristics which specify the non-correspondence (this usually involves making predictions and producing actions which may be more or less appropriate), iv) development in us of a new body of weighted assumptions now competent to correspond to the formerly non-correspondent features of the situation, and v) feed-back of information respecting the appropriateness and inappropriateness of our newly adjusted predictions and action. These requirements include more specific insights which parallel the learning paradigm given earlier.

(i) The nervous system is built for action. This action is always expressive of the dynamic flux purposes obtaining within the organism. The nervous system is integrated in the function of its parts and as a whole. Recurrent patterns of stimuli impinging from the outside may be represented and re-represented in central patterns, but always in conservative relationship to previously established ongoing patterns and in conformity to presently obtaining purposes.

IMPLICATIONS RELATING TO NATIONAL GOVERNMENT AND DIPLOMACY

Here, we intend considering national adaptability and national growth in the light of implications arising from our consideration of individual existences. The first and most obvious recommendation contributed by the analogy is the need to establish and identify integrated national purposes. The purposes of a nation like those of an individual are manifold and always in flux. Some are short-term and others long-range. National purposes demand purposeful dedication and responsibility among the nation's citizens and its allies, public identification of individual and group accomplishments in the light of national purposes, and some means for the expression of national satisfaction in the development and exercise of national capabilities. A wise nation, like a wise individual, has worthy goals, defined in terms of positive, broad and long-range growth potentialities. The ultimate achievement of any nation depends not only upon its creation of institutions embodying national ideals and its level of national aspiration and self-respect but depends, in large measure, upon the degree of aspiration and self-discipline exercised by its servants and citizens. The pursuit of national excellence, like the pursuit of individual excellence, is an ennobling and liberating as well as disciplining enterprise.

A nation, like a man wishing to be understood, identifies and displays its purposes so as to aid others to understand and anticipate appropriately its national actions. Narrow and negative purposes, and purposes inadequately projected, represent

handicaps in communication. This is especially important to bear in mind because purposes affect foreign as well as national perceptions, judgments and actions. National purposes expressed for export and conveyed internally should be entirely congruent. As with an individual, the flux of national purposes contain conflicts. This may call for alternation of efforts in support of contrasting short-term purposes. Yet it is important never to lose sight of the long-range purposes and to keep moving in that general direction.

It would seem appropriate in a nation, as in an individual, to find means to direct attention to non-correspondences between national assumptions and predictions based on past experience and the actual sequence of events. As with an individual, discovery of such non-correspondences is difficult. First, it is frustrated by the assumption that the behavior of other nations and national representatives will be consistent according to our limited impression of their world-view, judgments and actions. Second, the discovery of non-correspondences is frustrated by any national influence in the direction of a national conformity of views. The goal in attending to non-correspondences is to become as fully aware as possible of all of the characteristics of objective reality. We need not be blind, nationally. But this requires a positive policy of cultivating persons able to perceive, and encourage to perceive, non-correspondences between our national percepts, ideas and acts and the actual circumstances obtaining. There is a positive national need for persons who understand the previous experiences of other nations so thoroughly that they are enabled to make better predictions than those based on our own characteristic national sets of assumptions and purposes. It takes positive national purpose to be receptive and responsive to evidences of non-correspondence.

A third requirement is for abundant and spirited activity on a national scale; activity which acknowledges the inevitability of change; activity which recognizes the processes of becoming on a national scale. The nation should have the zest to utilize the potentialities offered by change rather than to suffer passively from the limitations imposed by change. National activity must correspond with the evolution and achievement of national purposes, to the perception of "national self" and the "national self" in relation to the rest of the world. National activity must relate to the refinement and adjustment of national perspectives, national concepts and national ideals; national activity must be wisely balanced by rational insight into the fact that it is impossible to succeed one hundred per cent of the time, that it may be more deadly to be afraid of making mistakes than to make them. There must be a national willingness to act tentatively, to utilize what turns out to be inappropriate action as a key to growth, to be internally and externally candid about misdirected and incorrect interpretations and actions and, on occasion, to withhold action in favor of a theoretical testing out of alternatives in the search for a more desirable course of action Such

a trial of alternatives will give insight into more dimensions than can be discovered simply by the traditional techniques of defining predictions on the basis of past national experience.

We need a national scheme of working assumptions based upon objectively evaluated past experiences projected realistically into the future, weighted according to present and projected needs of the nation. This scheme should be open-ended, plastic and modifiable. It should be as objectively oriented to reality as possible through a continuing testing against events as they evolve. The scheme will reveal many non-correspondences but it should not itself be considered infallible. The chief difficulty will lie in keeping the scheme of working assumptions sufficiently dynamic and future-oriented.

There is a continuing need for the collection of objective information as to the success or failure of the communication of national purposes. This is no easy objective for either an individual or a nation but any degree of its achievement acts correctively on the contents of conscious awareness. Both an individual and a nation have internal appetites and aspirations impelling actions which might be quite inappropriate in the objective circumstances. The only safeguard resides in having institutional mechanisms for objectifying information concerning outside relations. As with the individual, this is encouraged by maximizing interactions. I suppose that a nation may suffer from isolation from the rest of the world in some ways analogous to an individual in a sensory deprivation experiment. In such circumstances, we might expect patterns based on past experience to interfere with incoming signals and with the objectification of national self-awareness.

Science can play a particular role in relation to national security and welfare according to this scheme. First, it is the professional business of science to discover non-correspondences. Science makes headway when it discovers discrepancies between its present limited concepts and the behavior of nature. The techniques of science are directed toward the objectification of these discoveries and their interpretation and application in the largest and most general sense.

Second, science characteristically builds models and makes internal trial-and-error exercises. Sometimes these are entirely mental processes; often they involve elaborate equipment. By means of experiments, scientists attempt to grasp the significant relations of natural phenomena without having to replicate nature in its entirety. Science can play an important role in the testing of alternative perceptions, judgments and activities and in the selection of techniques prior to the undertaking of expensive and committing national actions.

Third, science continually practices the development of schemes of weighted assumptions which are as far as possible generalized to include all sensory experiences, both past and future. These are open-ended schemes of science, always accessible to new evidence of non-correspondence.

As a system of thought, science is unique in requiring maximum intellectual freedom, in not being imposed by coercion or persuasion, and in not being destroyed when found internally inconsistent. Paradoxically, science becomes stronger and more coherent as its limited views are made manifest. The search for Scientific Truth (which can never be realized) becomes increasingly powerful as error is discovered in lesser scientific truths. A lie in science cannot persist for it will be found out through the continuing activities of science. As noted earlier, scientists can be invited to seek truths of advantage to one nation and disadvantage to other nations; or they can be invited to seek truths of advantage relating to the longest range interests of mankind as a whole. In either direction, science can out-challenge and out-perform any other technique of approach.

Already science has outstripped all other forces affecting business, law and politics. In the near future, equally powerful influences will be recognizable throughout biological, psychological and social affairs. Just as man learned through invention and, later, through science and technology that he did not have to submit to nature "in the raw," he will soon find that in areas of behavioral barbarism and international anarchy, science can equivalently liberate man from dependence upon chance and fate. Society has much to learn as to what science is not, what it cannot do, and what are the conditions that science requires. But, in competition with what science can do, traditional modes of action are clearly less adequate. The competition of science cannot be met by recourse to tradition.

Within the last decade there has been an intellectual convergence of many scientific disciplines: psychology and the social sciences, cybernetics (including techniques for operations research and systems analysis), ethology, embryology, neuroanatomy, neurophysiology, neurochemistry and pharmacology, and comparative studies involving many of these disciplines have rather abruptly begun to contribute meaningfully to one another. There still exist barriers interfering with effective interdisciplinary communication. Some of these are conditioned disciplinary differences capable of resolution. Each discipline follows traditions laid down by its own intellectual forebears at a time when there could have been little hope for conceptual transaction with other disciplines. Some barriers to intellectual interchange are more obstinate, such as that caused by the massiveness and esotery of specialized domains of scientific literature. Each discipline represents a corps of scientists striving hard to

learn truths about processes which overlap with the other disciplines. Each has much to contribute toward the resolution of our must urgent national needs. Most of all, the congeries of science need the guidance of high national purpose.

Parallel with this convergence of research devotion among several related disciplines has been the establishment of institutions dedicated to their support as conjoined enterprises and of individuals trained in the no man's land between previously isolated disciplines. The entire atmosphere is one of rapidly changing long-range perspectives. What is confidently to be anticipated from these trends is the development of a more inclusive and coherent view of human economy and relations. But as compared with the magnitude and acuity of the great problems facing mankind, the present effort is far too little. This is the first non-correspondence which needs to be recognized on a national scale and to be followed up in purposeful action. We hope the effort will not indefinitely remain too little and we hope it will not be too late. Time and intellectual manpower and other resources must be increasingly resolutely devoted to progress in understanding human relations and national relations in all their dimensions: progress toward the solution of our most urgent national problems is dependent upon conceptual advances peculiarly susceptible to derivation through the activities of science.

GENERAL CONSIDERATIONS

Administration means ministrations to. It connotes a stewardship rather than an option of power. Its accomplishments are to be measured in terms of services rendered toward the achievement of the larger objectives of an organization. There is no significance to the measurement of administrative accomplishments in terms of any other activity. The evaluation of administration must be made according to headway the organization makes in the direction of its long-range goals and not according to the degree of conformity to administrative principles considered apart from this context of mission. Too easily we fall into the habit of following the "right procedure" at the expense of seeking fulfillment of the mission.

These truths seem self-evident; but like many fundamental truths they are so general as to be readily overlooked in practice. Neglect of these principles leads to the cynicism that that administration is best which administers least. This is untrue. That administration is best which administers best. It is possible to appreciate this fact, on a relative scale, by comparing one administration with another or with an ideal conception of administration.

Administration needs continually to be strengthened and revivified in courage and ingenuity in the way of moving the organization forward toward fulfillment of its mission. Administration is not an equilibrium-seeking device. It needs to anticipate and prepare for what the organization is going to require and not simply to respond to emergencies as they arise.

Specifically, this means, in the intramural research programs of the National Institutes of Health, that we must arrange our resources of space, personnel, time and equipment so as to yield the greatest saltatory advances toward understanding health and disease. We need to attract and keep the best brains in all of the cogent fields of biomedical knowledge and research. We need to insure that they will recognize this environment as a community of scholars created for the purpose of intellectual endeavor; that the first administrative as well as professional priority is for creative persons to address themselves to the solution of health problems, broadly conceived. If this is not obviously the first priority goal, and if it is not clearly demonstrated in all administrative actions, we are in need of overhauling. Not everyone must be a full blown genius to participate worthily in the accomplishment of this mission; geniuses are only too rare. But creative genius is the indispensible ingredient of any organization that aspires to bring forth new knowledge. Highly creative persons are likely to be attracted to wherever there are the greatest opportunities for intellectual growth and development. This means that the National Institutes of Health must provide an environment clearly equal to or better than any other environment in the competition for talent that is indispensible to our best accomplishments. Even more suitable than this competitive goal is the aim to achieve an ideal research and educational environment that can be a model for all other institutions. In the last few years, the National Institutes of Health has been looking outward and striving to project such models through its extramural supports; in the course of this worthy objective, the Institutes have relatively neglected the competitive standing of their own programs in Bethesda.

A more adequate understanding of biomedical problems cannot be achieved in the abstract; it is brought about through the consideration of materials with which the creative scientist is already familiar. Even the most gifted and energetic person must acquire and sustain mastery in the field of his unfolding accomplishments. This is why the educational programs at the National Institutes of Health are so important. The scientist must have a keen sense of what needs to be done to solve a given problem and he must command the skill to do that. He must carry out a program of thought and action at the limits of conception. And he must then follow through by communicating in a clear way his new level of understanding.

Every significant step toward the development of a new concept is bound to seem alien and eccentric. The processes of creative accomplishment are not entirely under voluntary control. They require from the scientist a thorough understanding of the problem, discipline and hard work and, in addition, the exercise of combinatory play of abstract imagery that requires the highest personal devotion and, in addition, freedom from interruptions and distractions. Truly creative contributions in science cannot be squeezed out as paste is extruded from a tube, simply through manipulating technical materials in an environment urging productivity. Even too pressing a desire to arrive quickly at logically connected ideas may foreshorten or divert altogether the conceptual contributions of which a competent scientist may otherwise be fully capable. On this account, discipline of the creative process must come from within the individual; coming from outside the individual, discipline of the creative process can only be provided through example.

Success in fulfilling the mission of the intramural research program of the National Institutes of Health will depend upon this kind of intellectual and conceptual progress. The professional reputation of the Institutes will depend upon the realization of such progress. There is no other way.

Robert B. Livingston, M. D.

ANNUAL REPORT - NARRATIVE SUMMARY

NIMH Addiction Research Center
PHS Hospital, Lexington, Kentucky

For the Period 1 January to 31 December 1960

I. General and Administrative

General. The mission of the NIMH Addiction Research Center is the conduct of research on the causes, prevention, and treatment of drug addiction. Although this may seem a narrow scientific field to many persons, it is actually a broad area. Many years of experience has shown that addiction is a very complex phenomenon with pharmacological, physiological, biochemical, socio-environmental and psychological components. The study of addiction is much more than the study of a few types of drugs. Addiction has roots in the neuroses and behavior disorders, and is therefore related to the entire field of human behavior. The work of the Addiction Research Center is pertinent not only to drug addiction specifically, but to the broad area of nervous and mental disease in general.

Thus the section on opiate addiction carries on studies of the addictiveness of new analgesics, partly, as a service function to prevent introduction of potentially addictive materials into clinical use without sufficient and proper warning. Despite the time required for this routine task, the section

was able to develop new methods for evaluating quantitatively the subjective responses following administration of opiates. The methods are simple, can be carried out by ordinary ward personnel, correlate well with the objective physical manifestations created by the drugs, and they constitute in fact a prototype technique generally applicable in clinical psychopharmacology. Simultaneously, a more sophisticated approach to evaluation of the subjective effects of drugs has been carried on by the psychological staff. Inventories have been developed which differentiate between different types of drugs and yield quantitative dose responses. Factor analyses of the data show that the information gathered in the inventory is not only useful in the evaluation of different drugs, but may also yield data of fundamental importance to the psychological modes of action of the various drugs.

The most interesting drug studied by the section on opiates during the year was a compound developed in the Hoffman-La Roche Laboratories at Basle, Switzerland -- 1-(p-Chlor-phenethyl)-2-methyl-6, 7-dimethoxy-1, 2, 3, 4-tetrahydro-isoquinoline hydrochloride (NIH-7672A, or ARC I-K-1). Adequately controlled clinical studies have shown that this drug is at least as effective as codeine in relieving pain when administered either intramuscularly or orally. Unlike other analgesics, I-K-1 does not induce clearcut morphine-like subjective effects of any intensity in former morphine addicts following administration of the highest doses that can safely be given. It is only a very weak suppressor of abstinence from morphine, being only

1/7th as potent as codeine in this respect. It does not induce a significant degree of physical dependence following administration of the highest doses compatible with safety for 30 days or more. This compound may represent the greatest dissociation between analgesia and physical addictive properties than has yet been achieved.

Experiments on the effects of drugs on the electroencephalographic and peripheral vasopressor responses to stimulation of the midbrain reticular formation, carried out by the neurophysiological section, have led to hypotheses that both "muscarinic" (blocked by atropine) and adrenergic synapses are involved in these responses. Alternative pathways may exist which take over the function of the primary pathways when either the muscarinic or adrenergic synapses are blocked. These concepts may be of fundamental importance in neurophysiology, and alternative pathways may be involved in tolerance to drugs.

The psychological unit continued work designed to elucidate psychological mechanisms involved in pain and its relief, a project obviously of great significance to clinical medicine in general. Work was initiated on probability learning in psychopaths, in the hope that light may be shed on the reasons for this puzzling pattern of behavior which is important in the areas of alcoholism and delinquency as well as in the field of opiate addiction. The psychological unit also continued work on conditioning factors of possible importance in relapse to opiate drugs.

A modest beginning was made on problems of alcohol. It consisted of elucidation and quantitation of the subjective effects of alcohol in human subjects and comparison of these with the effects of other centrally active drugs in the same patients. Also pertinent to the problem of alcohol was the project carried out in the neurophysiological section on the mechanisms of convulsions and delirium following withdrawal of barbiturates and related drugs. This study suggests that the cerebral cortex is not necessary for the development of withdrawal convulsions.

Administrative. The administrative workload of the entire Addiction Research Center has continued to grow due to the addition of more scientific personnel and to the gradual assumption of many of the functions formerly carried out by the administrative section of the hospital. Despite the increased workload, the administrative staff under the efficient leadership of Mrs. Ruth Nordstrom continued to conserve effectively the time of the scientific personnel.

The morale of the personnel within the Addiction Research Center continued at its previous high level throughout the year. Electronic engineer, John N. Schneider, left the unit in order to do his required military time in the Air Force. It is hoped he will return to us following completion of his tour of duty.

Due to Dr. Wikler's absence for a year of training, the services of a psychologist GS-5, Herbert D. Smith, were no longer required. He was replaced by a clerk-transcription machine operator GS-4, because of the

need for additional stenographic assistance within the administrative unit. Two temporary employees performed maintenance services for half of the calendar year.

Psychologist Harris E. Hill was promoted to supervising psychologist, GS-14, Harold G. Flanary to physicist GS-13, O. A. Kelly to assistant supervising aide GS-6, and C. A. Haertzen to clinical psychologist GS-11. C. W. Stivers came on duty as medical aide GS-5, and Vivian L. Jennings took the position of clerk-transcription machine operator GS-4. The position of biochemist-enzymologist GS-13 remains unfilled. A highly recommended prospect visited the unit during November, and it is hoped that he will accept the position.

Mrs. Luella R. Wainscott, library assistant, received a superior performance award, Dr. A. J. Eisenman was appointed a member of the Committee of Experts for the United Nations' program of opium research, four members of the staff were elected to the Kentucky Academy of Sciences, and Dr. H. Isbell became editor-in-chief for the United States and Canada, of Psychopharmacologia, during Dr. Wikler's absence.

Five members of the staff presented lectures on addiction and psychopharmacology at nine medical schools. The demand for teaching services is becoming so heavy that a local policy, putting some definite limitation on the amount of teaching, may have to be developed.

In addition to teaching in medical schools, Drs. C. F. Essig, A. Wikler, H. F. Fraser, W. R. Martin and H. Isbell all participated in the residency training program of the hospital. Consultative services in neurology, electroencephalography, internal medicine, and withdrawal ward management continued to be furnished to the hospital.

Dr. Harris Isbell spent the last half of his year of training (January-June 1960) in London. He visited a large number of medical schools and institutions and made many contacts with British scientists working in neuropharmacology and in psychopharmacology. He also gave several lectures to various British institutions, including university lecture on "The Pharmacology of Opiate Addiction," Kings College, University of London, and the Eighth Kelynack Memorial Lecture, on "Perspectives in Research on Opiate Addiction," before the British Society for the Study of Addiction.

Dr. Abraham Wikler left for Europe the latter part of June for a year of study and training. He has had a very successful half-year and has visited many laboratories in Switzerland, Scandinavia, and the low countries. He delivered, by invitation, a lecture on "Survey of Research on Alcohol at the Addiction Research Center" at the 26th International Congress on Alcoholism, in Stockholm, Sweden, 31 July 1960. He has, in addition, delivered lectures at various universities and institutions in Great Britain.

The most pressing physical need of the Addiction Research Center is about to be met -- an appropriation of $350,000 was approved by the Congress for construction of a basic research building. Preliminary plans for the building and the site have now been approved by NIMH and the Division of Hospitals, and it is hoped that architectural contract will soon be let and detailed planning completed in time to break ground for the building in March or April 1961.

II. Studies on Addictive Properties of New Analgesics

These studies are designed primarily for the purpose of providing information on the human addiction liabilities of new drugs (chiefly potent analgesics) with morphine-like properties for use by authorities responsible for recommending measures for control of such agents at national and international levels. They also assist the medical profession in evaluation of the therapeutic and toxic properties of new drugs in clinical use, and provide opportunities for basic research on the mechanisms of tolerance, addiction, and habituation.

During the current year improvements were made in methodology for measuring the overall abuse-liability of new drugs. Thus "subjective" and "objective" rating scales of behavioral change (with particular reference to "euphoria") were tested for several new drugs under double-blind conditions. As noted in the last annual report, these quantitative data revealed a high degree of concordance between the ratings of our experimental subjects ("subjective") and the ratings of the observers ("objective") in the case of

the potent analgesics such as morphine and heroin, but considerable discordance when weaker analgesics were tested. The addictive "ratings" of opiate addicts for a series of morphine-like drugs, respecting the parameters (1) identification as "dope" (opiate), (2) "strength" (potency), and (3) the extent to which they "would like to take each drug daily" covaried with the intensity of the abstinence syndrome which developed when each of these drugs was discontinued abruptly. The degree of "acceptance" of drugs by addicts was significantly influenced by the route of administration; for example, positive "acceptance" of morphine orally was zero, 40 per cent when given subcutaneously, and 54 per cent by the intravenous route. Heroin had an "acceptance" rating of 32 per cent subcutaneously as compared to 76 per cent intravenously.

Since addicts in the United States prefer to take their drugs intravenously, an intensive comparison was made of intravenous morphine and heroin, using single doses and four levels of each drug in order to obtain the relative potency of each. In addition, both morphine and heroin were administered intravenously to postaddicts in an 18-day direct addiction test. All studies utilized a "cross-over," "double-blind" design. Using a variety of objective and subjective measures, it was found that 1 mg of heroin was equivalent to 1.80 to 2.66 mg of morphine sulfate. Postaddicts could identify morphine and heroin as such with a high degree of accuracy when these

agents were administered intravenously, either acutely or chronically. Though they showed no preference for a single injection of one or the other of these drugs, they expressed a preference for heroin in the short-term addiction study (76 per cent positive "acceptance" for heroin, and 54 per cent for morphine).

Addictiveness of seven new synthetic analgesic compounds. In the text, Addiction Research Center numbers (ARC) or generic names will be used to designate compounds.

1. 1-(p-Chlor-phenethyl)-2-methyl-6, 7-dimethoxy-1, 2, 3, 4-tetrahydro-isoquinoline HCl (NIH-7672A, ARC I-K-1)

This is a new isoquinoline derivative reported to have analgesic potency in man comparable to that of codeine, but tests in postaddicts show its addictiveness is less than that of codeine, and even less than that of d-propoxyphene. This means that it shows a favorable dissociation between analgesic and addictiveness. Clinically it would probably be satisfactory only for oral use because it is very insoluble and a potent tissue irritant when injected, a feature which greatly reduces its abuse liability.

When given orally to former addicts, I-K-1 did not induce euphoria nor suppress abstinence in morphine dependent patients, nor did it induce any detectable degree of physical dependence when administered on an addictive schedule for 60 days. Although it partially suppressed abstinence when given intramuscularly, it was only about 1/7th as potent as codeine in this respect, and such large doses of an acid solution were required that

protracted inflammation at the site of injection ensued. In single intravenous doses of 60 and 120 mg it induced subjective effects somewhat similar to those of comparable doses of codeine, but it was not feasible to administer intravenous doses repeatedly because of chemical thrombosis of the veins; hence any danger of addictiveness by the intravenous route is minimal. Work on I-K-1 has been completed and will be reported to the Committee on Drug Addiction and Narcotics of the National Research Council, and prepared for publication.

2. 2-(Beta-hydroxyphenethylamino)-pyridine . Hcl (Phenyramidol, ARC I-L-1, and
3. N-Isopropyl-2-methyl-2-propyl-1, 3-propanediol dicarbamate (Carisoprodol, ARC I-M-1)

Phenyramidol and carisoprodol will be described together. They were investigated because both were alleged to be internuncial neuronal blockers and both compounds were being marketed as orally effective muscle relaxants with analgesic properties.

Phenyramidol showed no evidence of addictive properties.

Carisoprodol, in large single doses, induced barbiturate-like effects; it partially but significantly suppressed abstinence in doses of 15 to 20 times the dose of morphine; and, although tolerance to sedative effects developed in the direct addiction tests, it was not identified as an opiate by former morphine addicts and there was no abstinence syndrome when the drug was discontinued abruptly. Carisoprodol has less addictiveness than codeine and d-propoxyphene.

Work on phenyramidol and carisoprodol is complete and will be reported to the Committee on Drug Addiction and Narcotics, NRC.

4. Alpha-dl-3-acetoxy-4, 4-diphenyl-6-methylaminoheptane hydrochloride (NIH-7667, ARC I-C-25)

This is a derivative of methadone. Subcutaneously it is more potent than morphine in inducing morphine-like euphoria and in suppressing abstinence from morphine. A report to this effect will be made to the Committee on Drug Addiction and Narcotics, NRC.

5. 6-Acetyl-3 ethoxydihydromorphine (NIH-7623, ARC I-A-38)

This compound is related structurally to both morphine and heroin. Subcutaneous doses of 100 to 200 mg induced consistent morphine-like effects and it was about one-half as effective as morphine in suppressing abstinence. It is considered to have abuse liability greater than that of codeine but possibly less than that of morphine. A report to this effect will be made to the Committee on Drug Addiction and Narcotics, NRC.

6. N-(1-Methyl-2-piperidinoethyl)-propioanilide . Hcl (NIH-7602, ARC I-I-1, Phenampromid), and

7. N-(2[Methyl)-phenethylamino]-propyl)-propioanilide (NIH-7603, ARC I-J-1, Diampromid)

Phenampromid or diampromid administered orally induced morphine-like subjective effects and behavior in nontolerant former morphine addicts, and both suppressed symptoms of abstinence from morphine.

A report on phenampromid and diampromid was made to the Committee on Drug Addiction and Narcotics, NRC, in January 1960. The Committee advised the Commissioner of Narcotics that both compounds should be placed under control of the narcotic laws of the United States. The President, after appropriate action by the Commissioner, promulgated an order to this effect in October 1960.

III. Acute and Chronic Intoxication with Drugs Other than Analgesics, Barbiturates or Alcohol.

1. Cross tolerance between LSD and psilocybin.

Two experiments were completed during the year. In the first, 10 subjects received LSD in doses increasing to 1.5 mcg/kg over a 6-day period, and on another occasion the same patients received psilocybin in doses increasing to 150 mcg/kg over the same period of time. The patients were then tested with the drug they had been receiving, and "challenged" with the drug they had not been receiving. In the second experiment, 9 patients received LSD in doses increasing to 1.5 mcg/kg over a period of 12 days, and on another occasion, psilocybin in doses increasing to 210 mcg/kg over a period of 12 days, following which they were tested with the drug they had been receiving and "challenged" with the converse drug. The second experiment was carried out to determine if administration of psilocybin over a longer period of time would result in a higher degree of cross tolerance to LSD. The results in both experiments were similar. Definite tolerance to psilocybin developed in both experiments, as manifested by the reduction in

both "objective" and "subjective" parameters of response. The patients tolerant to psilocybin also showed a reduced response to LSD. Conversely patients tolerant to LSD also showed a reduced response to psilocybin. Direct tolerance to LSD was greater in degree than direct tolerance to psilocybin. Increasing the dose and length of time over which psilocybin was administered did not increase the degree of tolerance and cross tolerance. This demonstration of cross tolerance between the two drugs reinforces the hypothesis, which was based on the similarity of the clinical patterns of effects induced by both, that they induce psychic aberrations by acting through common mechanisms or through mechanisms serving a final common pathway. The study suggests that psychotomimetic drugs can be classified into definite groups by studying tolerance and cross tolerance.

2. Cross tolerance between LSD and mescaline.

As the initial step in this project, a comparison has been made of the objective and subjective effects of LSD and mescaline in 10 patients. Patterns of effects induced by both drugs were very similar. Objective findings after both included elevation of temperature, elevation of blood pressure, diminution in threshold for the kneejerk, and pupillary dilatation. Subjective reports after both drugs included anxiety, feeling of unreality, perceptual distortion (particularly visual), and hallucinations. LSD is approximately three-thousand times as potent as mescaline. Cross-tolerance experiments between both drugs will be completed early in 1961.

3. Psilocin.

This compound is simply dephosphorylated psilocybin. Its effects, in comparison with those of mescaline and LSD, were studied in 10 men. In the doses and manner used, it proved to be the most reliable psychotomimetic drug we have ever studied. All 10 patients who received 150 mcg/kg of psilocin intramuscularly developed marked symptoms of depersonalization, vivid visual hallucinations, and many of them lost insight. Onset of action of psilocin is extremely rapid and the effects are largely dissipated in less than four hours. Because of its short length of action, psilocin may be preferable to LSD or mescaline as a psychotherapeutic tool or as a possible psychodiagnostic agent.

IV. Clinical Studies of Intoxication with Alcohol, Barbiturates, and Related Drugs.

During the year work progressed on the psychopathology of alcoholism as compared with that of narcotic addiction, on acute effects of alcohol and barbiturates on verbal report, and on testing for possible correlations between such drug effects and personality characteristics. Previously reported were findings on the first application of factor analysis to personality profiles (MMPI) of three institutionalized groups, 200 alcoholics, 200 narcotic addicts, and 200 criminals. This analysis indicated considerable similarity of these populations, especially with regard to psychopathic traits. During the present year an inverted, rectangular factor analysis was applied, using all profiles to check and refine previous results. From

these analyses emerged five factors similar to those found earlier but more clearly defined. The first and common factor, on which practically all profiles regardless of group were heavily loaded, was interpreted as social deviance. The characteristic was so strong in the three populations that no factor independent of such psychopathic traits was found. In Factors 2, 3, 4 and 5 the dominating influence of social deviance was combined with various neurotic and schizoid tendencies, none of which however were sufficiently differentiating to even approach diagnostic significance. This study, for which early publication is planned, strongly suggests that psychopathy or social deviance is of specific etiological significance to neither alcoholism nor narcotic addiction, nor is it of such significance for the addictions in general. However it does appear that such measures as were used in the study are general predictors of asocial or antisocial actions, including addictions of various sorts. Predictors of the specific directions of such behavior apparently must be sought elsewhere, perhaps they may still be sought partially within the framework of social deviance, with emphasis on the level of availability of deviant modes of action and on the lack or impairment of behavioral controls which result in such deviancy.

Measurement of subjective effects of three doses of alcohol and one of pentobarbital in acute studies were continued, using the Addiction Research Center Inventory (ARCI). Previous pilot work had established a dose of pentobarbital, and initial and maintaining doses of alcohol which produced appropriate intoxication for a period of about three hours. During the year,

gathering of data on the main study was completed. The data were analyzed in the same manner as those discussed under Psychological Studies of Addiction (see VII below). Two scales of discriminating items were developed for both alcohol and pentobarbital (3.00 cc/kg of 30% alcohol with maintaining doses, and 200 mg of pentobarbital). Publication of the studies as separates and in manual form is anticipated. Work is also going forward, by means of correlational and other techniques, to ascertain common and specific effects of these drugs within the limits of the ARCI. Administration of the Guilford-Zimmerman Temperament Survey to post-addicts, under conditions of no-drug and the above dose of alcohol, failed to support Eysenck's theory concerning the actions of alcohol on individuals showing different degrees of introversion-extroversion. Significant correlations were found on four scales of this survey. They indicate that the emotionally labile, depressed individual is most strongly affected by alcohol. These data are to be reanalyzed before being prepared for publication. Other personality-drug effect correlations will be implemented as ARCI data are collated with those from the MMPI.

V. Biochemistry of Addiction

Excretion of heroin and codeine.

Since the toxicology laboratory of the University of Wisconsin and this laboratory encounter some of the same problems concerning the routine analyses of urines of suspected addicts for the detection of opium alkaloids and related drugs, it was thought that a joint study would be mutually beneficial. The purpose of the study was to determine just how long and how much morphine could be detected in the urine of subjects possessing high and low tolerance to heroin after abrupt withdrawal of the drug, and how much and how long morphine, codeine, and other codeine metabolites could be detected in the urine of subjects possessing high and low tolerance to codeine. Extraction and chromatography methods devised by Dr. G. J. Mannering were used for the study.

The unexpected finding that nicotine has the same R_f as morphine in the chromatography solvent system used for the heroin experiment necessitated a change in the proposed procedure for the quantitative assay of the chromatograms for morphine. Much time was spent in developing a method that excluded nicotine. A method of eluting the chromatograms and reacting with silicomolybdic acid which gave suitable recoveries, without interference from nicotine, was eventually devised. Our half of the duplicate samples from the heroin study have been quantitated, however, the results are not reported herein since Dr. Mannering has not completed his samples. The

codeine phase of the experiment has been completed through the initial extraction procedure, and will be finished when Dr. Mannering decides on the best procedure to follow for the final quantitation of the residues.

Opiate and synthetic drugs excreted in urines submitted by the clinical service.

The introduction of routine chromatography in the tests for urinary morphine has resulted in tests which are free of interference from newly introduced drugs. Urinary demerol has been separated by chromatography into demerol and nor-demerol.

VI. Neurophysiology and Neuropharmacology of Chronic Intoxication of Barbiturates and Related Drugs

Elevation of electrical seizure thresholds.

Daily induction of convulsions by slowly increasing the voltage of the stimulating electrical currents until a fit ensues results in a progressive increase in the voltage necessary for production of a convulsion ("ECT" tolerance). Such tolerance occurred in adrenalectomized animals maintained on fixed amounts of adrenal corticosteroids and therefore is not likely due to increased adrenal cortical activity arising from the stress of repeated convulsions. If one pair of stimulating electrodes are implanted anteriorly and another pair posteriorly, daily stimulation of the anterior pair results in increase of the threshold through the posterior pair, even though stimulation is applied to the posterior pair at intervals widely separated in time. This suggests a general cerebral change rather than a focal change directly beneath the stimulating electrodes.

The project is to be continued. If elevation of the ECT threshold can be induced in rats by daily stimulation through corneal electrodes, the rate of progress can be accelerated. It will become possible to determine whether daily electrostimulation results in an increased production of a hypothetical chemical by the brain which is a "natural" anticonvulsant.

Effects of bilateral decortication on barbiturate withdrawal convulsions.

Three totally decorticated dogs and one decorticated cat did not have grand mal seizures following abrupt withdrawal of barbiturates after long intoxication, whereas all unoperated controls did have convulsions. Thus it seems that the cerebral cortex is necessary for grand mal seizures during withdrawal of barbiturates. Pentylenetetrazole (metrazole) induced typical grand mal convulsions in a totally decorticated dog. Determinations of the amounts of pentylenetetrazole required for the induction of convulsions in decorticated dogs and their controls should be necessary before a clear interpretation can be made.

These investigations are to be continued, using higher dose levels of barbiturates and longer periods of chronic intoxication. In addition, electrical recordings from subcortical structures will be made in order to determine whether barbiturate withdrawal seizures originate in subcortical structures. In the latter case, the effect of decortication might be due to simple elevation in the threshold for grand mal convulsions.

Effect of dilantin on barbiturate withdrawal convulsions.

Maximum tolerated doses of dilantin orally, intraperitoneally and intravenously did not prevent convulsions due to abstinence from barbiturates in chronically intoxicated dogs. Further pharmacological analysis of the mechanisms of barbiturate withdrawal convulsions will be carried out, using such drugs as scopolamine, physostigmine, and sodium hydrazide.

Effect of unilateral cerebral cortical lesions on the occurrence of convulsions during withdrawal of barbiturates from small dogs.

Barbiturate withdrawal convulsions did not occur in any of 4 animals in which focal cerebral cortical lesions were induced by injection of either aluminum hydroxide cream or by freezing with ethyl chloride. Convulsions did occur in the controls. The project is to be continued utilizing higher doses of barbiturates, other species of animals such as rats and monkeys, the effect of topically applied acetylcholine during withdrawal of barbiturates, and the thresholds for direct cortical responses to electrical stimulation during abstinence from barbiturates.

VII. Psychological Studies of Addiction

Gathering and analysis of data on the Addiction Research Inventory for differentiating subjective effects of drugs continued to be the main clinical study of drug actions in psychology. This work has been progressing for several years through construction of a 550-item inventory from an original pool of 3400 questions (by means of exploratory work on this pool with various drugs) to development of various drug scales. The final form of the inventory was printed and administered to approximately 175 postaddict subjects under the following conditions: no-drug, placebo, morphine, alcohol (4 dose levels), pentobarbital, chlorpromazine, LSD-25 (2 dose levels), amphetamine, and pyrahexyl compound (2 dose levels). All individuals were also given two different personality inventories and a test of literacy and intelligence. During 1960, gathering of data was completed. The data from subjects who produced valid tests, as indicated by a rational scale of consistency, were transcribed to punchcards and processed in various ways by the Computing Center of the University of Kentucky.

By means of an item analysis all other conditions were compared with placebo on a first group of 50 subjects. This method uses the frequencies of "true" and "false" responses, and a technique for determining statistical significance to isolate all items of the inventory which discriminate separately between placebo and every other condition at or beyond the 0.05 percent level. These procedures resulted in initial scales of differentiating items or questions. Similar data on a second group of 50 subjects were

processed in the same manner. Items were then chosen for the final scales which maintained discrimination in both groups at less than the 0.05-per cent level of significance. These final scales were then tested on a third group of 30 subjects for purposes of validity generalization. Scales derived in this way were termed "primary," since they were composed of items showing the strongest drug effects. In addition, "secondary" scales were developed concurrently with the above. These scales consisted of items selected in the placebo and the other conditions in the same manner, but that differentiated placebo and the other conditions in the total at the 0.05-level of significance. Although only superficial analysis of scale content has been made, the primary scales appear to be heavily loaded with sensory and affective or mood changes, and alteration in the stimulation-depression continuum. The secondary scales are composed of items which appear not to be as physiologically-based. However in the case of LSD-25, the only drug to which factor analysis has been applied, it was found that apparently all "secondary" effects are dependent upon the occurrence of the "primary" effects. Such inter-relationships are to be investigated in the other drug conditions. Separate publication is anticipated for each of the developed drug scales. These initial publications and the preparation of a test manual, however, cannot include detailed analyses of the actions of each drug and their inter-relationships. Such analyses of common, multiple, and specific drug actions have been started, but they are so complex and refractory to statistical techniques that they must be dealt with as individual

studies. Factor analysis is by no means ideal for most of the work, and development of original methods may be a necessity. The work of discovering possible correlations between drug-effects and personality characteristics is also one of the main objectives of these investigations. Preliminary work is encouraging, but sustained effort must await completion of several other phases in this area. As time and personnel permit, the ARC Inventory will be standardized on normal populations with and without drug medication. It will be used for investigating alcoholism and schizophrenia, and should be especially useful in measuring psychopathy or social deviance.

Other studies on human subjects continued during the year included the gathering of Minnesota Multiphasic Personality Inventory profiles on physician addicts, and investigations of probability learning in former addicts. Both have progressed rather slowly but for different reasons. Previously, addict physicians were tested 30 days or more after their admission to the hospital. For some unknown reason, the number of available subjects was not maintained at the rate found in the earlier part of the study. Testing at 10 days after admission during the past year was instituted to facilitate gathering of an adequate sample, and to compare such profiles with those obtained after 30 days. The study is being continued for the next year, but prospects are not encouraging because of the current low admission rate.

The probability learning study, which is now in progress, is one of a number of different procedures which will be directed toward comparing variables which control decision making and thus behavior in the "psychopath" and normal subject. Is the behavior of the psychopath controlled to a greater extent by immediate rather than remote contingencies, by negative rather than positive reinforcements, and more nearly by immediate personal gratification and relief from frustrations than is the behavior of the "normal" individual? As appropriate procedures are developed for answering these questions, drug produced alterations in the controlling variables will be introduced. During 1960 data were gathered on 60 subjects, using a probability learning procedure. This study was postponed to allow collection of data on the ARC Inventory, and the addition of several more groups is necessary to draw more than tentative conclusions. The procedure involves an estimate or prediction of future events in a simple situation where one of three lights will be lit. The task of the subject is to predict which light will be lit on successive trials. His only source of information is his experience in the situation. He does not know that the separate lights are presented 70, 20, and 10 per cent of the trials in randomized order. Data accumulated to date indicate that addicts overestimate the most frequent alternative and underestimate the least frequent. Thus far this finding is the opposite to that found in normals. Also such "choice" behavior in the addict is altered in the direction of "normalcy" by administration of appropriate doses of morphine. Various other types of reinforcement will be used under control and drug conditions.

In rats, the practical and theoretical aspects of anxiety reduction by potent analgesic drugs were pursued further. This series of studies was originally begun on human subjects to test the hypothesis that reduction of pain-conditioned anxiety is a necessary action of potent analgesics, and to develop a method for detecting such drugs. A very promising procedure was devised and published. The theoretical basis for the study was strongly supported. Continued work with this procedure in man was not feasible since it was very penalizing to the subjects and to the experimenter as well, because it was necessary that he test the apparatus on himself. An animal method was then set up which complemented the human work and involved the same general principles. Rats were trained to press a lever in a Skinner-box to obtain food. A 4-minute tone terminated by a brief, strong electric shock was applied to the feet of the rat during each daily session. Shortly, the tone acquired an inhibiting function, producing cessation of lever-pressing for its duration. This inhibition was assumed to represent the effects of pain-conditioned anxiety or a conditioned emotional response (CER). It was then hypothesized that potent analgesics would reduce this form of inhibition, as had occurred in man, and that other classes of drugs would not. Work on this technique, which extended over several years and which is being continued in modified form, was completed on 10 drugs in multiple doses. It was found that opioids produced significant dose-effect curves of CER reduction; optimal doses practically eliminated effects of the tone. Significant dose-effect curves were found for no other drug except

pentobarbital and then only at 20 minutes after injection. Effects of drugs other than these two classes are to some extent dependent upon the intensity of the tone and other parameters. Publication of several papers on this CER work is being postponed until ancillary studies clarify further the actions of pertinent drugs on auditory discrimination, sufficient work on other supplementary procedures having already been completed. In this work the most encouraging procedure is the imposition of a tone discrimination upon an escape response. Apparently this type of conditioning has never been accomplished previously. Shock intensity is extremely critical. The rat runs from an electrified start box, down a short alley to escape in one of two end boxes. Tone is in one end box, signalling the "hot," or non-escape side. Apparently no discrimination involving choice can be established when the shock is at such a level as to be a prepotent stimulus. In the limited number of animals that have thus far been successfully conditioned in this way, when using optimal doses found in the CER work, morphine and pentobarbital abolish avoidance behavior, raise the "escape" shock level, but have no effect on discriminative escape, while amphetamine has an effect on only the latter, disrupting it. These studies of the CER and ancillary investigations may be of considerable practical and theoretical value in several different areas other than pain and analgesia.

Interoceptive conditioning has been studied little in the United States and such endeavors have been sporadic. It would appear that at least some behavioral effects of drugs can be reasonably subsumed under such learning or conditioning principles. Work on the actions of drugs at the ARC assumes that one mechanism by which drugs produce effects on behavior is through alteration of internal stimuli. Such changes may produce effects in behavior by facilitating or inhibiting responses directly, or drug-produced changes in the organism may come to act as occasions for responses in their own right, i.e., become stimuli to which responses are conditioned (The studies to be described later, on a pharmacodynamic theory of relapse to narcotic drugs, are partially based upon such reasoning). Previous annual reports summarized studies on rats in which support for such a position was obtained and in which amphetamine was found to act as a "depressant" rather than a stimulant. Initial work in rats on the effects of autonomic blocking agents was also described. Studies on the latter are being continued. The hypothesis being tested is that while autonomic effector activity is not essential for the acquisition of a traumatic avoidance response, such activity serves to increase resistance of the response to extinction. To test this hypothesis, acquisition and extinction of a traumatic avoidance response under non-medicated conditions are compared with these procedures under the ganglionic blocking agent Ecolid. Because there is hazard in assuming that drugs always act according to published descriptions, it was necessary to demonstrate initially that Ecolid is an autonomic blocking

drug. After several tedious and discouraging pilot studies, partially shown in the previous report, a procedure was found which demonstrated that Ecolid does significantly reduce blood pressure in the otherwise unmedicated rat. To our knowledge this is the first demonstration of such effects. A method was then devised for producing traumatic avoidance conditioning. As yet the experimental design has not been completed, about half of the groups remain to be tested. However, the data show (contrary to expectation) that Ecolid slightly impairs conditioning to asymptotic performance, but does indeed hasten markedly the extinction or "dropping-out" of the traumatic response. As shown in other studies, shock intensity during conditioning is an important parameter in determining the strength of the conditioned response as measured by resistance to extinction. In this study the least effect of the drug was found on extinction after conditioning on the highest of three shock levels. This work is being continued. Investigations of this nature may have significance for predicting and therapeutically controlling emotion and some forms of mental illness.

VIII. The Mode of Action of Central Nervous System Depressants

During the last year work on the mode of action of drugs on brainstem integrating and regulatory mechanisms has been limited to investigations of acute tolerance and physical dependence on opiates in the dog and cat. Various aspects of these problems have been studied in the intact dog, the spinal dog, and the *cerveau isolé* cat.

In addition to evaluating the effect of morphine and nalorphine on behavioral states in intact and spinal dogs (e.g., sleep, sedation, restlessness, etc.), observations have been made on pulse rate, respiratory rate, body temperature, pupillary diameter, skin twitch, and withdrawal reflexes (intact dog), patellar reflex (S. D. - spinal dog), ipsilateral flexor reflex (S. D.), contralateral crossed extensor reflex (S. D.), and the extensor thrust reflex (S. D.). The effects of single subcutaneous doses of morphine sulfate (10 mg/kg) and nalorphine HC_1 (20 mg/kg) were evaluated for a 5-hour period following injection to provide a base line for the determination of tolerance and to evaluate morphine-nalorphine interactions in both intact and spinal dogs.

Morphine sulfate was infused at a rate of 3 mg/kg/hr in intact dogs for 7-1/2 to 8 hours. Maximum sedation was observed 2 to 3 hours after onset of infusion; thereafter dogs that had shown severe depression (no spontaneous activity and unresponsive to both nociceptive and non-painful stimuli) became progressively more responsive, and by the end of the infusion some dogs would stand, turn and walk spontaneously. A concomitant temporal pattern of alteration was seen for depression of the skin twitch, withdrawal reflex and miosis; these effects were maximal after two hours of infusion and thereafter diminished in magnitude. A 10 mg/kg subcutaneous test dose of morphine (17 hours (circa) after the end of infusion produeed a smaller degree of miosis and significantly less depression of the skin twitch and withdrawal reflex than this test dose did prior to infusion,

despite the fact that dogs had not completely recovered from the infused morphine, as evidenced by a subnormal pulse rate and body temperature. These findings indicated that tolerance developed during the course of infusion and was clearly demonstrable 17 hours after the end of infusion.

Administration of nalorphine (20 mg/kg) following a 7-1/2 to 8 hour infusion of morphine (3 mg/kg/hr) in the intact dog produces a syndrome which consists of marked restlessness, violent tremors, lacrimation, salivation, rhinorrhea, defecation, urination, acceleration of respiratory rate, marked tachycardia, mydriasis and a rapid increase in body temperature.

Nalorphine (20 mg/kg) produced,in the intact dog, only minimal changes, the most striking of which was miosis. Although nalorphine produced no discernible depression of the skin twitch or withdrawal reflexes in the intact dog, it produced a decided depression of the ipsilateral flexor and the crossed extensor reflexes in the spinal dog. These reflexes were even more profoundly depressed by morphine. No signs of recovery of these reflexes were observed in the spinal dog during an 8-hour infusion of morphine. In this respect, tolerance to the effect on reflex responses elicited by nociceptive stimulation in the spinal dog developed at a slower rate than did tolerance to morphine-induced alterations in reflexes evoked by nociceptive stimuli in the intact dog.

In the spinal dog, administration of nalorphine (20 mg/kg) following an 8-hour infusion of morphine (3 mg/kg/hr) evoked not only the above signs of abstinence, but in addition caused extensor hypertonus of the hindlegs, inhibited the extensor thrust reflex, increased the sensitivity for evocation of running movements in the hindlimbs and increased the magnitude of the crossed extensor and ipsilateral flexor reflexes above that observed following either nalorphine or morphine. These signs in the intact and spinal dog resemble abstinence signs observed in dogs chronically addicted to morphine and indicates that physical dependence can be consistently produced following a single infusion of morphine.

In elucidating the physiological factors responsible for signs of physical dependence, rapidly changing homeostatic levels seem to be of great importance. The cerveau isolé cat has been used to assess the effects of morphine, nalorphine, and morphine followed by nalorphine on the relationship between serum CO_2, serum pH, respiratory rate, and pulse rate. The cerveau isolé preparation has been used in this study to eliminate the effect of the hypothalamic thermoregulatory center on the respiratory mechanism.

Administration of morphine (20 mg/kg) to the feline cerveau isolé preparation depressed respiratory rate (e.g., RR 19 to 10), caused hypercapnia and increased serum pH slightly. Administration of nalorphine

(10 mg/kg) following morphine (20 mg/kg) produces a marked tachypnea (e.g., RR 10 to 35) which gradually diminishes to a modest increase in respiratory rate (2 or 3 breaths per minute over the control level), hypocapnia, and a slight but significant serum alkalosis.

The marked tachypnea observed when nalorphine was administered after morphine was accompanied by a tachycardia. These changes are part of the acute abstinence syndrome and can be explained by the fact that morphine depresses homeostatic level and creates a state in which the equilibrium-concentration of serum CO_2 is higher than in the control state. Administration of nalorphine rapidly shifts the homeostatic level back to the control level. The high serum levels of CO_2 now act as a potent stimulant to the respiratory and cardio-accelerator centers with resultant tachypnea and tachycardia.

IX. Conditioning Factors in Addiction and Habituation (Relapse)

The general theory and basic postulates around which this project was designed have been described elsewhere, and in some detail in previous annual reports. Briefly the theory states that, in part at least, relapse to addicting drugs represents a complex of responses which are conditioned to environmental stimuli (both external and internal) that were associated with periodic reduction of abstinence distress consequent to addiction. It is postulated that once physical dependence on a given drug is established, each dose of the drug serves to reinforce whatever behavior is instrumental in bringing about further administration of the drug, i.e., behavior which

results in obtaining the drug and thereby reduces objective and subjective signs of abstinence from the drug increases in probability of occurrence after each "successful" obtaining of drug as a result of the behavior. Furthermore it is postulated that the strength of such "primary" reinforcement, as well as the strength of "secondary" reinforcement by environmental stimuli regularly associated with the former, varies directly with the "effort" or "hustling" inherent in the performance of the instrumental responses. The complexity of primary and higher orders of reinforcement may be expected to greatly obscure the basis for inveterate recidivisms in man. It seemed reasonable to assume however that primary reinforcement of the sort described, as well as relatively simple secondary reinforcements, might well be used with animals to test hypotheses derived from the basic postulates.

Rats were used in previously described work, and are currently being utilized to obtain fundamental information before proceeding to use of primates. Studies are progressing on the two major and interesting aspects of the project. Pharmacological, and initial conditioning investigations of the actions of morphine and a more potent, faster acting opioid (the benzimidazole derivative known as I-G-2). The purposes of these studies are to test preference or aversive behavior to orally administered I-G-2 in nonaddicted rats, and in rats addicted by daily injections of morphine from which opioids are withheld for various periods of time; to develop valid and reliable methods of measuring tolerance to, and abstinence from

the above drugs; to determine the relative reinforcing value of ingested I-G-2 on the probability of pressing a Skinner-bar during cycles of addiction and abstinence from opioids.

In studies initiated previously it was shown that reliable evidence of physical dependence on morphine could be obtained only when the daily subcutaneous dose was maintained at 200 mg/kg. While this drug is a standard in many studies on the opioids, it is difficult to administer orally (or otherwise instrumentally) to rats, and by this route in rats lacks the fast onset of action which is essential for effective conditioning procedures. Thus in most of the conditioning and preference studies undertaken to date animals were maintained on 200 mg/kg of morphine subcutaneously daily, and consumption of I-G-2 and instrumental acts of obtaining it were used as the dependent variables. Studies completed or initiated during the year are described below.

One objective of the previous and current year was to determine whether rats could discriminate I-G-2 from water by taste (the work would be much simplified if it were shown that rats could not detect the substance over a wide range of concentrations that might be employed in subsequent investigations). In one study addicted and nonaddicted animals were deprived of water for 22 hours daily and were then permitted, through the use of appropriate "start" and "goal" cages, a choice of drinking either water or a 5-mcg/cc solution of I-G-2. Without training, neither of the groups showed preference nor aversion for either of the solutions. In a

second phase of this study distinctive cues were paired with I-G-2 and presented in the same way as above with water, in randomized right or left order. Both addicted and nonaddicted groups established a clear preference for I-G-2 with no significant differences occurring between groups as measured by amount of solution drunk. During extinction of the selective response to I-G-2, only non-significant trends were found. However in subsequent reinforcement and extinction trials in these addicted and nonaddicted rats, it was found that the addicted animals responded to short-term reinforcement, whereas the controls did not. Further studies for delineating preference and taste thresholds of I-G-2 in pressing a Skinner-bar, show that water deprived rats develop no aversion to ascending concentrations of 5, 10, 20, 30, 40, 50 or 60 mcg/cc. Thus these studies clearly indicated that I-G-2 is very appropriate for present purposes insofar as non-discrimination by taste is involved. In addition, these studies provided data showing that the effects of I-G-2 are similar to those of morphine, since the effects occurred within 4 to 9 minutes after commencement of drinking and partial evidence of cross tolerance between morphine and I-G-2. Addiction has been maintained in these rats by morphine injection (as mentioned, this is inconvenient and hazardous to animals). Studies are now started in which "direct addiction" to I-G-2 is being attempted by allowing rats free access to the liquid in their home cage instead of water. Thus far the concentrations have been 5 and 10 mcg/cc. The rats apparently maintain themselves well on these concentrations. They

show most of the signs of morphine addiction, and upon administration of nalorphine the few animals thus far tested exhibit mild abstinence signs similar to those found after morphine withdrawal. The I-G-2 concentrations will be increased to the point at which strong abstinence signs occur. Studies were also begun on instrumentation and procedures for obtaining greater validity and reliability in measuring the abstinence syndrome. This pharmacological work will consist of developing and applying apparatus for measuring precisely temperature changes, cardiac rate, oxygen consumption, and the recording of observational data during addiction and abstinence. Data thus gathered, in addition to being informative per se, will be used to determine time of peak abstinence, and thus the optimal point for use of I-G-2 as a reward or reinforcer in the behavioral studies.

Training or conditioning was an integral part of one of the above mentioned studies in which animals chose between drinking I-G-2 or water. Some indication of "relapse" to the drug was found. In another instrumental situation, addicted and control rats were conditioned to press a Skinner-bar for either I-G-2 or water under 22-hour water deprivation or 24-hour water satiation. Differential stimuli in the form of visual and tactile cues were presented with both liquids. After considerable training, reinforced bar-pressing of addicted animals exceeded that of nonaddicted rats on water-deprivation days irrespective of the liquid, whereas on water-satiation days the rates of addicted animals were significantly higher only when I-G-2 was the liquid obtained by bar-pressing. During tests in which the stabilization

dose of morphine was withheld, statistically significant intergroup differences in abstinence signs were found with peaking at the 72nd hour. In testing for "relapse," after all animals had been maintained on water only for 23 days, during which time morphine was withheld from the addicted animals, overall bar-pressing rates were found to be higher in the addicted animals. These trends appeared to be strong although not statistically significant. The latter appeared to be due to the small number of animals, several having died as a result of the morphine injections during maintained addiction.

In addition to the continuing studies mentioned, further conditioning investigations are progressing which use the Skinner-box, refined experimental design, and larger groups of both control and addicted rats. These experiments will supplement the preference and "relapse" data found previously. During the coming year a "rat-rotor" will be used by means of which different schedules of reinforcement by I-G-2 for bar-pressing can be automatically controlled. If rats can be maintained at a sufficiently high addiction level on orally administered I-G-2, the rat-rotor will be utilized for "self-addiction" purposes as well as for scheduling different periods of deprivation and integrating these with different reinforcement programs. It is anticipated that these experiments will provide information basic to the efficient initiation of studies using primates as subjects in work on conditioning factors in addiction and relapse.

X. Effect of Drug and Other Variables on "Mental Set"

This procedure, described in some detail in previous reports, may be regarded as a method for quantifying "attention." Extending this concept somewhat, the procedure as previously interpreted measures response "set" (readiness or disposition to respond). The relevance of the procedure for studying schizophrenia and for the actions of drugs on behavior depends on the findings of earlier investigators who found that certain indices of reaction time are among the most valid indicants of schizophrenia as compared with other mental illnesses. As described in previous reports, the procedure is a modification of that used by Huston and Singer (Arch. Neurol. Psychiat. 53: 365-369, 1945) for measuring auditory-manual reaction times. These are measured following visual "warning" signals at different foreperiods (the time between the warning signal and the signal to press a key) which are scheduled in "regular" and "irregular" orders. In previous years it was found that LSD-25, morphine, and pentobarbital produced changes in response set of non-psychotic postaddicts which were similar qualitatively but not quantitatively to those found in schizophrenic patients under no-drug conditions. The data on the above drugs, as well as on amphetamine, were transformed to insure homogeneity of variance, analyzed, and compared. Since that time groups of schizophrenics have been tested, and during the past year the effects of "fatigue" on set have been studied in both the addict and schizophrenic groups. The design used to isolate fatigue effects, which may influence reaction time in both groups

toward the "schizophrenic pattern," consisted of 1) comparing the first and the last 9 trials for each foreperiod series of the regular order, 2) comparing data gathered when the 2.0 second preceded the 3.5 foreperiod with data obtained when these periods were reversed, and 3) comparing reaction times found in the regular procedure when it was given first and when it was given after the irregular procedure. The data have multiplied to such an extent that analysis would be overwhelming if attempted manually. They have therefore been collated for processing by the Computing Center of the University of Kentucky (IBM-650). When the analyses are completed they will provide more clearly defined comparisons of "mental set" of schizophrenics and that of postaddicts under the above drugs, and the refined data will, at least in part, determine the extent to which the defect in set found in schizophrenia is due to alteration in the order of "warning" stimuli and to fatigue. Future work will depend in large part on the direction and significance uncovered by the computations.

ANNUAL REPORT - NARRATIVE SUMMARY

NIMH Addiction Research Center
PHS Hospital, Lexington, Kentucky

For the Period 1 January to 31 December 1960

I. General and Administrative

General. The mission of the NIMH Addiction Research Center is the conduct of research on the causes, prevention, and treatment of drug addiction. Although this may seem a narrow scientific field to many persons, it is actually a broad area. Many years of experience has shown that addiction is a very complex phenomenon with pharmacological, physiological, biochemical, socio-environmental and psychological components. The study of addiction is much more than the study of a few types of drugs. Addiction has roots in the neuroses and behavior disorders, and is therefore related to the entire field of human behavior. The work of the Addiction Research Center is pertinent not only to drug addiction specifically, but to the broad area of nervous and mental disease in general.

Thus the section on opiate addiction carries on studies of the addictiveness of new analgesics, partly, as a service function to prevent introduction of potentially addictive materials into clinical use without sufficient and proper warning. Despite the time required for this routine task, the section

was able to develop new methods for evaluating quantitatively the subjective responses following administration of opiates. The methods are simple, can be carried out by ordinary ward personnel, correlate well with the objective physical manifestations created by the drugs, and they constitute in fact a prototype technique generally applicable in clinical psychopharmacology. Simultaneously, a more sophisticated approach to evaluation of the subjective effects of drugs has been carried on by the psychological staff. Inventories have been developed which differentiate between different types of drugs and yield quantitative dose responses. Factor analyses of the data show that the information gathered in the inventory is not only useful in the evaluation of different drugs, but may also yield data of fundamental importance to the psychological modes of action of the various drugs.

The most interesting drug studied by the section on opiates during the year was a compound developed in the Hoffman-La Roche Laboratories at Basle, Switzerland -- 1-(p-Chlor-phenethyl)-2-methyl-6, 7-dimethoxy-1, 2, 3, 4-tetrahydro-isoquinoline hydrochloride (NIH-7672A, or ARC I-K-1). Adequately controlled clinical studies have shown that this drug is at least as effective as codeine in relieving pain when administered either intramuscularly or orally. Unlike other analgesics, I-K-1 does not induce clearcut morphine-like subjective effects of any intensity in former morphine addicts following administration of the highest doses that can safely be given. It is only a very weak suppressor of abstinence from morphine, being only

1/7th as potent as codeine in this respect. It does not induce a significant degree of physical dependence following administration of the highest doses compatible with safety for 30 days or more. This compound may represent the greatest dissociation between analgesia and physical addictive properties than has yet been achieved.

Experiments on the effects of drugs on the electroencephalographic and peripheral vasopressor responses to stimulation of the midbrain reticular formation, carried out by the neurophysiological section, have led to hypotheses that both "muscarinic" (blocked by atropine) and adrenergic synapses are involved in these responses. Alternative pathways may exist which take over the function of the primary pathways when either the muscarinic or adrenergic synapses are blocked. These concepts may be of fundamental importance in neurophysiology, and alternative pathways may be involved in tolerance to drugs.

The psychological unit continued work designed to elucidate psychological mechanisms involved in pain and its relief, a project obviously of great significance to clinical medicine in general. Work was initiated on probability learning in psychopaths, in the hope that light may be shed on the reasons for this puzzling pattern of behavior which is important in the areas of alcoholism and delinquency as well as in the field of opiate addiction. The psychological unit also continued work on conditioning factors of possible importance in relapse to opiate drugs.

A modest beginning was made on problems of alcohol. It consisted of elucidation and quantitation of the subjective effects of alcohol in human subjects and comparison of these with the effects of other centrally active drugs in the same patients. Also pertinent to the problem of alcohol was the project carried out in the neurophysiological section on the mechanisms of convulsions and delirium following withdrawal of barbiturates and related drugs. This study suggests that the cerebral cortex is not necessary for the development of withdrawal convulsions.

Administrative. The administrative workload of the entire Addiction Research Center has continued to grow due to the addition of more scientific personnel and to the gradual assumption of many of the functions formerly carried out by the administrative section of the hospital. Despite the increased workload, the administrative staff under the efficient leadership of Mrs. Ruth Nordstrom continued to conserve effectively the time of the scientific personnel.

The morale of the personnel within the Addiction Research Center continued at its previous high level throughout the year. Electronic engineer, John N. Schneider, left the unit in order to do his required military time in the Air Force. It is hoped he will return to us following completion of his tour of duty.

Due to Dr. Wikler's absence for a year of training, the services of a psychologist GS-5, Herbert D. Smith, were no longer required. He was replaced by a clerk-transcription machine operator GS-4, because of the

need for additional stenographic assistance within the administrative unit. Two temporary employees performed maintenance services for half of the calendar year.

Psychologist Harris E. Hill was promoted to supervising psychologist, GS-14, Harold G. Flanary to physicist GS-13, O. A. Kelly to assistant supervising aide GS-6, and C. A. Haertzen to clinical psychologist GS-11. C. W. Stivers came on duty as medical aide GS-5, and Vivian L. Jennings took the position of clerk-transcription machine operator GS-4. The position of biochemist-enzymologist GS-13 remains unfilled. A highly recommended prospect visited the unit during November, and it is hoped that he will accept the position.

Mrs. Luella R. Wainscott, library assistant, received a superior performance award, Dr. A. J. Eisenman was appointed a member of the Committee of Experts for the United Nations' program of opium research, four members of the staff were elected to the Kentucky Academy of Sciences, and Dr. H. Isbell became editor-in-chief for the United States and Canada, of Psychopharmacologia, during Dr. Wikler's absence.

Five members of the staff presented lectures on addiction and psychopharmacology at nine medical schools. The demand for teaching services is becoming so heavy that a local policy, putting some definite limitation on the amount of teaching, may have to be developed.

In addition to teaching in medical schools, Drs. C. F. Essig, A. Wikler, H. F. Fraser, W. R. Martin and H. Isbell all participated in the residency training program of the hospital. Consultative services in neurology, electroencephalography, internal medicine, and withdrawal ward management continued to be furnished to the hospital.

Dr. Harris Isbell spent the last half of his year of training (January-June 1960) in London. He visited a large number of medical schools and institutions and made many contacts with British scientists working in neuropharmacology and in psychopharmacology. He also gave several lectures to various British institutions, including university lecture on "The Pharmacology of Opiate Addiction," Kings College, University of London, and the Eighth Kelynack Memorial Lecture, on "Perspectives in Research on Opiate Addiction," before the British Society for the Study of Addiction.

Dr. Abraham Wikler left for Europe the latter part of June for a year of study and training. He has had a very successful half-year and has visited many laboratories in Switzerland, Scandinavia, and the low countries. He delivered, by invitation, a lecture on "Survey of Research on Alcohol at the Addiction Research Center" at the 26th International Congress on Alcoholism, in Stockholm, Sweden, 31 July 1960. He has, in addition, delivered lectures at various universities and institutions in Great Britain.

The most pressing physical need of the Addiction Research Center is about to be met -- an appropriation of $350,000 was approved by the Congress for construction of a basic research building. Preliminary plans for the building and the site have now been approved by NIMH and the Division of Hospitals, and it is hoped that architectural contract will soon be let and detailed planning completed in time to break ground for the building in March or April 1961.

II. Studies on Addictive Properties of New Analgesics

These studies are designed primarily for the purpose of providing information on the human addiction liabilities of new drugs (chiefly potent analgesics) with morphine-like properties for use by authorities responsible for recommending measures for control of such agents at national and international levels. They also assist the medical profession in evaluation of the therapeutic and toxic properties of new drugs in clinical use, and provide opportunities for basic research on the mechanisms of tolerance, addiction, and habituation.

During the current year improvements were made in methodology for measuring the overall abuse-liability of new drugs. Thus "subjective" and "objective" rating scales of behavioral change (with particular reference to "euphoria") were tested for several new drugs under double-blind conditions. As noted in the last annual report, these quantitative data revealed a high degree of concordance between the ratings of our experimental subjects ("subjective") and the ratings of the observers ("objective") in the case of

the potent analgesics such as morphine and heroin, but considerable discordance when weaker analgesics were tested. The addictive "ratings" of opiate addicts for a series of morphine-like drugs, respecting the parameters (1) identification as "dope" (opiate), (2) "strength" (potency), and (3) the extent to which they "would like to take each drug daily" covaried with the intensity of the abstinence syndrome which developed when each of these drugs was discontinued abruptly. The degree of "acceptance" of drugs by addicts was significantly influenced by the route of administration; for example, positive "acceptance" of morphine orally was zero, 40 per cent when given subcutaneously, and 54 per cent by the intravenous route. Heroin had an "acceptance" rating of 32 per cent subcutaneously as compared to 76 per cent intravenously.

Since addicts in the United States prefer to take their drugs intravenously, an intensive comparison was made of intravenous morphine and heroin, using single doses and four levels of each drug in order to obtain the relative potency of each. In addition, both morphine and heroin were administered intravenously to postaddicts in an 18-day direct addiction test. All studies utilized a "cross-over," "double-blind" design. Using a variety of objective and subjective measures, it was found that 1 mg of heroin was equivalent to 1.80 to 2.66 mg of morphine sulfate. Postaddicts could identify morphine and heroin as such with a high degree of accuracy when these

agents were administered intravenously, either acutely or chronically. Though they showed no preference for a single injection of one or the other of these drugs, they expressed a preference for heroin in the short-term addiction study (76 per cent positive "acceptance" for heroin, and 54 per cent for morphine).

Addictiveness of seven new synthetic analgesic compounds. In the text, Addiction Research Center numbers (ARC) or generic names will be used to designate compounds.

1. 1-(p-Chlor-phenethyl)-2-methyl-6, 7-dimethoxy-1, 2, 3, 4-tetrahydro-isoquinoline HCl (NIH-7672A, ARC I-K-1)

This is a new isoquinoline derivative reported to have analgesic potency in man comparable to that of codeine, but tests in postaddicts show its addictiveness is less than that of codeine, and even less than that of d-propoxyphene. This means that it shows a favorable dissociation between analgesic and addictiveness. Clinically it would probably be satisfactory only for oral use because it is very insoluble and a potent tissue irritant when injected, a feature which greatly reduces its abuse liability.

When given orally to former addicts, I-K-1 did not induce euphoria nor suppress abstinence in morphine dependent patients, nor did it induce any detectable degree of physical dependence when administered on an addictive schedule for 60 days. Although it partially suppressed abstinence when given intramuscularly, it was only about 1/7th as potent as codeine in this respect, and such large doses of an acid solution were required that

protracted inflammation at the site of injection ensued. In single intravenous doses of 60 and 120 mg it induced subjective effects somewhat similar to those of comparable doses of codeine, but it was not feasible to administer intravenous doses repeatedly because of chemical thrombosis of the veins; hence any danger of addictiveness by the intravenous route is minimal. Work on I-K-1 has been completed and will be reported to the Committee on Drug Addiction and Narcotics of the National Research Council, and prepared for publication.

2. 2-(Beta-hydroxyphenethylamino)-pyridine . Hcl (Phenyramidol, ARC I-L-1, and
3. N-Isopropyl-2-methyl-2-propyl-1, 3-propanediol dicarbamate (Carisoprodol, ARC I-M-1)

Phenyramidol and carisoprodol will be described together. They were investigated because both were alleged to be internuncial neuronal blockers and both compounds were being marketed as orally effective muscle relaxants with analgesic properties.

Phenyramidol showed no evidence of addictive properties.

Carisoprodol, in large single doses, induced barbiturate-like effects; it partially but significantly suppressed abstinence in doses of 15 to 20 times the dose of morphine; and, although tolerance to sedative effects developed in the direct addiction tests, it was not identified as an opiate by former morphine addicts and there was no abstinence syndrome when the drug was discontinued abruptly. Carisoprodol has less addictiveness than codeine and d-propoxyphene.

Work on phenyramidol and carisoprodol is complete and will be reported to the Committee on Drug Addiction and Narcotics, NRC.

4. Alpha-dl-3-acetoxy-4, 4-diphenyl-6-methylaminoheptane hydrochloride (NIH-7667, ARC I-C-25)

This is a derivative of methadone. Subcutaneously it is more potent than morphine in inducing morphine-like euphoria and in suppressing abstinence from morphine. A report to this effect will be made to the Committee on Drug Addiction and Narcotics, NRC.

5. 6-Acetyl-3 ethoxydihydromorphine (NIH-7623, ARC I-A-38)

This compound is related structurally to both morphine and heroin. Subcutaneous doses of 100 to 200 mg induced consistent morphine-like effects and it was about one-half as effective as morphine in suppressing abstinence. It is considered to have abuse liability greater than that of codeine but possibly less than that of morphine. A report to this effect will be made to the Committee on Drug Addiction and Narcotics, NRC.

6. N-(1-Methyl-2-piperidinoethyl)-propioanilide . Hcl (NIH-7602, ARC I-I-1, Phenampromid), and
7. N-(2[Methyl)-phenethylamino]-propyl)-propioanilide (NIH-7603, ARC I-J-1, Diampromid)

Phenampromid or diampromid administered orally induced morphine-like subjective effects and behavior in nontolerant former morphine addicts, and both suppressed symptoms of abstinence from morphine.

A report on phenampromid and diampromid was made to the Committee on Drug Addiction and Narcotics, NRC, in January 1960. The Committee advised the Commissioner of Narcotics that both compounds should be placed under control of the narcotic laws of the United States. The President, after appropriate action by the Commissioner, promulgated an order to this effect in October 1960.

III. Acute and Chronic Intoxication with Drugs Other than Analgesics, Barbiturates or Alcohol.

1. Cross tolerance between LSD and psilocybin.

Two experiments were completed during the year. In the first, 10 subjects received LSD in doses increasing to 1.5 mcg/kg over a 6-day period, and on another occasion the same patients received psilocybin in doses increasing to 150 mcg/kg over the same period of time. The patients were then tested with the drug they had been receiving, and "challenged" with the drug they had not been receiving. In the second experiment, 9 patients received LSD in doses increasing to 1.5 mcg/kg over a period of 12 days, and on another occasion, psilocybin in doses increasing to 210 mcg/kg over a period of 12 days, following which they were tested with the drug they had been receiving and "challenged" with the converse drug. The second experiment was carried out to determine if administration of psilocybin over a longer period of time would result in a higher degree of cross tolerance to LSD. The results in both experiments were similar. Definite tolerance to psilocybin developed in both experiments, as manifested by the reduction in

both "objective" and "subjective" parameters of response. The patients tolerant to psilocybin also showed a reduced response to LSD. Conversely patients tolerant to LSD also showed a reduced response to psilocybin. Direct tolerance to LSD was greater in degree than direct tolerance to psilocybin. Increasing the dose and length of time over which psilocybin was administered did not increase the degree of tolerance and cross tolerance. This demonstration of cross tolerance between the two drugs reinforces the hypothesis, which was based on the similarity of the clinical patterns of effects induced by both, that they induce psychic aberrations by acting through common mechanisms or through mechanisms serving a final common pathway. The study suggests that psychotomimetic drugs can be classified into definite groups by studying tolerance and cross tolerance.

2. Cross tolerance between LSD and mescaline.

As the initial step in this project, a comparison has been made of the objective and subjective effects of LSD and mescaline in 10 patients. Patterns of effects induced by both drugs were very similar. Objective findings after both included elevation of temperature, elevation of blood pressure, diminution in threshold for the kneejerk, and pupillary dilatation. Subjective reports after both drugs included anxiety, feeling of unreality, perceptual distortion (particularly visual), and hallucinations. LSD is approximately three-thousand times as potent as mescaline. Cross-tolerance experiments between both drugs will be completed early in 1961.

3. Psilocin.

This compound is simply dephosphorylated psilocybin. Its effects, in comparison with those of mescaline and LSD, were studied in 10 men. In the doses and manner used, it proved to be the most reliable psychotomimetic drug we have ever studied. All 10 patients who received 150 mcg/kg of psilocin intramuscularly developed marked symptoms of depersonalization, vivid visual hallucinations, and many of them lost insight. Onset of action of psilocin is extremely rapid and the effects are largely dissipated in less than four hours. Because of its short length of action, psilocin may be preferable to LSD or mescaline as a psychotherapeutic tool or as a possible psychodiagnostic agent.

IV. Clinical Studies of Intoxication with Alcohol, Barbiturates, and Related Drugs.

During the year work progressed on the psychopathology of alcoholism as compared with that of narcotic addiction, on acute effects of alcohol and barbiturates on verbal report, and on testing for possible correlations between such drug effects and personality characteristics. Previously reported were findings on the first application of factor analysis to personality profiles (MMPI) of three institutionalized groups, 200 alcoholics, 200 narcotic addicts, and 200 criminals. This analysis indicated considerable similarity of these populations, especially with regard to psychopathic traits. During the present year an inverted, rectangular factor analysis was applied, using all profiles to check and refine previous results. From

these analyses emerged five factors similar to those found earlier but more clearly defined. The first and common factor, on which practically all profiles regardless of group were heavily loaded, was interpreted as social deviance. The characteristic was so strong in the three populations that no factor independent of such psychopathic traits was found. In Factors 2, 3, 4 and 5 the dominating influence of social deviance was combined with various neurotic and schizoid tendencies, none of which however were sufficiently differentiating to even approach diagnostic significance. This study, for which early publication is planned, strongly suggests that psychopathy or social deviance is of specific etiological significance to neither alcoholism nor narcotic addiction, nor is it of such significance for the addictions in general. However it does appear that such measures as were used in the study are general predictors of asocial or antisocial actions, including addictions of various sorts. Predictors of the specific directions of such behavior apparently must be sought elsewhere, perhaps they may still be sought partially within the framework of social deviance, with emphasis on the level of availability of deviant modes of action and on the lack or impairment of behavioral controls which result in such deviancy.

Measurement of subjective effects of three doses of alcohol and one of pentobarbital in acute studies were continued, using the Addiction Research Center Inventory (ARCI). Previous pilot work had established a dose of pentobarbital, and initial and maintaining doses of alcohol which produced appropriate intoxication for a period of about three hours. During the year,

gathering of data on the main study was completed. The data were analyzed in the same manner as those discussed under Psychological Studies of Addiction (see VII below). Two scales of discriminating items were developed for both alcohol and pentobarbital (3.00 cc/kg of 30% alcohol with maintaining doses, and 200 mg of pentobarbital). Publication of the studies as separates and in manual form is anticipated. Work is also going forward, by means of correlational and other techniques, to ascertain common and specific effects of these drugs within the limits of the ARCI. Administration of the Guilford-Zimmerman Temperament Survey to post-addicts, under conditions of no-drug and the above dose of alcohol, failed to support Eysenck's theory concerning the actions of alcohol on individuals showing different degrees of introversion-extroversion. Significant correlations were found on four scales of this survey. They indicate that the emotionally labile, depressed individual is most strongly affected by alcohol. These data are to be reanalyzed before being prepared for publication. Other personality-drug effect correlations will be implemented as ARCI data are collated with those from the MMPI.

V. Biochemistry of Addiction

Excretion of heroin and codeine.

Since the toxicology laboratory of the University of Wisconsin and this laboratory encounter some of the same problems concerning the routine analyses of urines of suspected addicts for the detection of opium alkaloids and related drugs, it was thought that a joint study would be mutually beneficial. The purpose of the study was to determine just how long and how much morphine could be detected in the urine of subjects possessing high and low tolerance to heroin after abrupt withdrawal of the drug, and how much and how long morphine, codeine, and other codeine metabolites could be detected in the urine of subjects possessing high and low tolerance to codeine. Extraction and chromatography methods devised by Dr. G. J. Mannering were used for the study.

The unexpected finding that nicotine has the same R_f as morphine in the chromatography solvent system used for the heroin experiment necessitated a change in the proposed procedure for the quantitative assay of the chromatograms for morphine. Much time was spent in developing a method that excluded nicotine. A method of eluting the chromatograms and reacting with silicomolybdic acid which gave suitable recoveries, without interference from nicotine, was eventually devised. Our half of the duplicate samples from the heroin study have been quantitated, however, the results are not reported herein since Dr. Mannering has not completed his samples. The

codeine phase of the experiment has been completed through the initial extraction procedure, and will be finished when Dr. Mannering decides on the best procedure to follow for the final quantitation of the residues.

Opiate and synthetic drugs excreted in urines submitted by the clinical service.

The introduction of routine chromatography in the tests for urinary morphine has resulted in tests which are free of interference from newly introduced drugs. Urinary demerol has been separated by chromatography into demerol and nor-demerol.

VI. Neurophysiology and Neuropharmacology of Chronic Intoxication of Barbiturates and Related Drugs

Elevation of electrical seizure thresholds.

Daily induction of convulsions by slowly increasing the voltage of the stimulating electrical currents until a fit ensues results in a progressive increase in the voltage necessary for production of a convulsion ("ECT" tolerance). Such tolerance occurred in adrenalectomized animals maintained on fixed amounts of adrenal corticosteroids and therefore is not likely due to increased adrenal cortical activity arising from the stress of repeated convulsions. If one pair of stimulating electrodes are implanted anteriorly and another pair posteriorly, daily stimulation of the anterior pair results in increase of the threshold through the posterior pair, even though stimulation is applied to the posterior pair at intervals widely separated in time. This suggests a general cerebral change rather than a focal change directly beneath the stimulating electrodes.

The project is to be continued. If elevation of the ECT threshold can be induced in rats by daily stimulation through corneal electrodes, the rate of progress can be accelerated. It will become possible to determine whether daily electrostimulation results in an increased production of a hypothetical chemical by the brain which is a "natural" anticonvulsant.

Effects of bilateral decortication on barbiturate withdrawal convulsions.

Three totally decorticated dogs and one decorticated cat did not have grand mal seizures following abrupt withdrawal of barbiturates after long intoxication, whereas all unoperated controls did have convulsions. Thus it seems that the cerebral cortex is necessary for grand mal seizures during withdrawal of barbiturates. Pentylenetetrazole (metrazole) induced typical grand mal convulsions in a totally decorticated dog. Determinations of the amounts of pentylenetetrazole required for the induction of convulsions in decorticated dogs and their controls should be necessary before a clear interpretation can be made.

These investigations are to be continued, using higher dose levels of barbiturates and longer periods of chronic intoxication. In addition, electrical recordings from subcortical structures will be made in order to determine whether barbiturate withdrawal seizures originate in subcortical structures. In the latter case, the effect of decortication might be due to simple elevation in the threshold for grand mal convulsions.

Effect of dilantin on barbiturate withdrawal convulsions.

Maximum tolerated doses of dilantin orally, intraperitoneally and intravenously did not prevent convulsions due to abstinence from barbiturates in chronically intoxicated dogs. Further pharmacological analysis of the mechanisms of barbiturate withdrawal convulsions will be carried out, using such drugs as scopolamine, physostigmine, and sodium hydrazide.

Effect of unilateral cerebral cortical lesions on the occurrence of convulsions during withdrawal of barbiturates from small dogs.

Barbiturate withdrawal convulsions did not occur in any of 4 animals in which focal cerebral cortical lesions were induced by injection of either aluminum hydroxide cream or by freezing with ethyl chloride. Convulsions did occur in the controls. The project is to be continued utilizing higher doses of barbiturates, other species of animals such as rats and monkeys, the effect of topically applied acetylcholine during withdrawal of barbiturates, and the thresholds for direct cortical responses to electrical stimulation during abstinence from barbiturates.

VII. Psychological Studies of Addiction

Gathering and analysis of data on the Addiction Research Inventory for differentiating subjective effects of drugs continued to be the main clinical study of drug actions in psychology. This work has been progressing for several years through construction of a 550-item inventory from an original pool of 3400 questions (by means of exploratory work on this pool with various drugs) to development of various drug scales. The final form of the inventory was printed and administered to approximately 175 postaddict subjects under the following conditions: no-drug, placebo, morphine, alcohol (4 dose levels), pentobarbital, chlorpromazine, LSD-25 (2 dose levels), amphetamine, and pyrahexyl compound (2 dose levels). All individuals were also given two different personality inventories and a test of literacy and intelligence. During 1960, gathering of data was completed. The data from subjects who produced valid tests, as indicated by a rational scale of consistency, were transcribed to punchcards and processed in various ways by the Computing Center of the University of Kentucky.

By means of an item analysis all other conditions were compared with placebo on a first group of 50 subjects. This method uses the frequencies of "true" and "false" responses, and a technique for determining statistical significance to isolate all items of the inventory which discriminate separately between placebo and every other condition at or beyond the 0.05 percent level. These procedures resulted in initial scales of differentiating items or questions. Similar data on a second group of 50 subjects were

processed in the same manner. Items were then chosen for the final scales which maintained discrimination in both groups at less than the 0.05-per cent level of significance. These final scales were then tested on a third group of 30 subjects for purposes of validity generalization. Scales derived in this way were termed "primary," since they were composed of items showing the strongest drug effects. In addition, "secondary" scales were developed concurrently with the above. These scales consisted of items selected in the placebo and the other conditions in the same manner, but that differentiated placebo and the other conditions in the total at the 0.05-level of significance. Although only superficial analysis of scale content has been made, the primary scales appear to be heavily loaded with sensory and affective or mood changes, and alteration in the stimulation-depression continuum. The secondary scales are composed of items which appear not to be as physiologically-based. However in the case of LSD-25, the only drug to which factor analysis has been applied, it was found that apparently all "secondary" effects are dependent upon the occurrence of the "primary" effects. Such inter-relationships are to be investigated in the other drug conditions. Separate publication is anticipated for each of the developed drug scales. These initial publications and the preparation of a test manual, however, cannot include detailed analyses of the actions of each drug and their inter-relationships. Such analyses of common, multiple, and specific drug actions have been started, but they are so complex and refractory to statistical techniques that they must be dealt with as individual

studies. Factor analysis is by no means ideal for most of the work, and development of original methods may be a necessity. The work of discovering possible correlations between drug-effects and personality characteristics is also one of the main objectives of these investigations. Preliminary work is encouraging, but sustained effort must await completion of several other phases in this area. As time and personnel permit, the ARC Inventory will be standardized on normal populations with and without drug medication. It will be used for investigating alcoholism and schizophrenia, and should be especially useful in measuring psychopathy or social deviance.

Other studies on human subjects continued during the year included the gathering of Minnesota Multiphasic Personality Inventory profiles on physician addicts, and investigations of probability learning in former addicts. Both have progressed rather slowly but for different reasons. Previously, addict physicians were tested 30 days or more after their admission to the hospital. For some unknown reason, the number of available subjects was not maintained at the rate found in the earlier part of the study. Testing at 10 days after admission during the past year was instituted to facilitate gathering of an adequate sample, and to compare such profiles with those obtained after 30 days. The study is being continued for the next year, but prospects are not encouraging because of the current low admission rate.

The probability learning study, which is now in progress, is one of a number of different procedures which will be directed toward comparing variables which control decision making and thus behavior in the "psychopath" and normal subject. Is the behavior of the psychopath controlled to a greater extent by immediate rather than remote contingencies, by negative rather than positive reinforcements, and more nearly by immediate personal gratification and relief from frustrations than is the behavior of the "normal" individual? As appropriate procedures are developed for answering these questions, drug produced alterations in the controlling variables will be introduced. During 1960 data were gathered on 60 subjects, using a probability learning procedure. This study was postponed to allow collection of data on the ARC Inventory, and the addition of several more groups is necessary to draw more than tentative conclusions. The procedure involves an estimate or prediction of future events in a simple situation where one of three lights will be lit. The task of the subject is to predict which light will be lit on successive trials. His only source of information is his experience in the situation. He does not know that the separate lights are presented 70, 20, and 10 per cent of the trials in randomized order. Data accumulated to date indicate that addicts overestimate the most frequent alternative and underestimate the least frequent. Thus far this finding is the opposite to that found in normals. Also such "choice" behavior in the addict is altered in the direction of "normalcy" by administration of appropriate doses of morphine. Various other types of reinforcement will be used under control and drug conditions.

In rats, the practical and theoretical aspects of anxiety reduction by potent analgesic drugs were pursued further. This series of studies was originally begun on human subjects to test the hypothesis that reduction of pain-conditioned anxiety is a necessary action of potent analgesics, and to develop a method for detecting such drugs. A very promising procedure was devised and published. The theoretical basis for the study was strongly supported. Continued work with this procedure in man was not feasible since it was very penalizing to the subjects and to the experimenter as well, because it was necessary that he test the apparatus on himself. An animal method was then set up which complemented the human work and involved the same general principles. Rats were trained to press a lever in a Skinner-box to obtain food. A 4-minute tone terminated by a brief, strong electric shock was applied to the feet of the rat during each daily session. Shortly, the tone acquired an inhibiting function, producing cessation of lever-pressing for its duration. This inhibition was assumed to represent the effects of pain-conditioned anxiety or a conditioned emotional response (CER). It was then hypothesized that potent analgesics would reduce this form of inhibition, as had occurred in man, and that other classes of drugs would not. Work on this technique, which extended over several years and which is being continued in modified form, was completed on 10 drugs in multiple doses. It was found that opioids produced significant dose-effect curves of CER reduction; optimal doses practically eliminated effects of the tone. Significant dose-effect curves were found for no other drug except

pentobarbital and then only at 20 minutes after injection. Effects of drugs other than these two classes are to some extent dependent upon the intensity of the tone and other parameters. Publication of several papers on this CER work is being postponed until ancillary studies clarify further the actions of pertinent drugs on auditory discrimination, sufficient work on other supplementary procedures having already been completed. In this work the most encouraging procedure is the imposition of a tone discrimination upon an escape response. Apparently this type of conditioning has never been accomplished previously. Shock intensity is extremely critical. The rat runs from an electrified start box, down a short alley to escape in one of two end boxes. Tone is in one end box, signalling the "hot," or non-escape side. Apparently no discrimination involving choice can be established when the shock is at such a level as to be a prepotent stimulus. In the limited number of animals that have thus far been successfully conditioned in this way, when using optimal doses found in the CER work, morphine and pentobarbital abolish avoidance behavior, raise the "escape" shock level, but have no effect on discriminative escape, while amphetamine has an effect on only the latter, disrupting it. These studies of the CER and ancillary investigations may be of considerable practical and theoretical value in several different areas other than pain and analgesia.

Interoceptive conditioning has been studied little in the United States and such endeavors have been sporadic. It would appear that at least some behavioral effects of drugs can be reasonably subsumed under such learning or conditioning principles. Work on the actions of drugs at the ARC assumes that one mechanism by which drugs produce effects on behavior is through alteration of internal stimuli. Such changes may produce effects in behavior by facilitating or inhibiting responses directly, or drug-produced changes in the organism may come to act as occasions for responses in their own right, i.e., become stimuli to which responses are conditioned (The studies to be described later, on a pharmacodynamic theory of relapse to narcotic drugs, are partially based upon such reasoning). Previous annual reports summarized studies on rats in which support for such a position was obtained and in which amphetamine was found to act as a "depressant" rather than a stimulant. Initial work in rats on the effects of autonomic blocking agents was also described. Studies on the latter are being continued. The hypothesis being tested is that while autonomic effector activity is not essential for the acquisition of a traumatic avoidance response, such activity serves to increase resistance of the response to extinction. To test this hypothesis, acquisition and extinction of a traumatic avoidance response under non-medicated conditions are compared with these procedures under the ganglionic blocking agent Ecolid. Because there is hazard in assuming that drugs always act according to published descriptions, it was necessary to demonstrate initially that Ecolid is an autonomic blocking

drug. After several tedious and discouraging pilot studies, partially shown in the previous report, a procedure was found which demonstrated that Ecolid does significantly reduce blood pressure in the otherwise unmedicated rat. To our knowledge this is the first demonstration of such effects. A method was then devised for producing traumatic avoidance conditioning. As yet the experimental design has not been completed, about half of the groups remain to be tested. However, the data show (contrary to expectation) that Ecolid slightly impairs conditioning to asymptotic performance, but does indeed hasten markedly the extinction or "dropping-out" of the traumatic response. As shown in other studies, shock intensity during conditioning is an important parameter in determining the strength of the conditioned response as measured by resistance to extinction. In this study the least effect of the drug was found on extinction after conditioning on the highest of three shock levels. This work is being continued. Investigations of this nature may have significance for predicting and therapeutically controlling emotion and some forms of mental illness.

VIII. The Mode of Action of Central Nervous System Depressants

During the last year work on the mode of action of drugs on brainstem integrating and regulatory mechanisms has been limited to investigations of acute tolerance and physical dependence on opiates in the dog and cat. Various aspects of these problems have been studied in the intact dog, the spinal dog, and the *cerveau isolé* cat.

In addition to evaluating the effect of morphine and nalorphine on behavioral states in intact and spinal dogs (e.g., sleep, sedation, restlessness, etc.), observations have been made on pulse rate, respiratory rate, body temperature, pupillary diameter, skin twitch, and withdrawal reflexes (intact dog), patellar reflex (S. D. - spinal dog), ipsilateral flexor reflex (S. D.), contralateral crossed extensor reflex (S. D.), and the extensor thrust reflex (S. D.). The effects of single subcutaneous doses of morphine sulfate (10 mg/kg) and nalorphine HC_1 (20 mg/kg) were evaluated for a 5-hour period following injection to provide a base line for the determination of tolerance and to evaluate morphine-nalorphine interactions in both intact and spinal dogs.

Morphine sulfate was infused at a rate of 3 mg/kg/hr in intact dogs for 7-1/2 to 8 hours. Maximum sedation was observed 2 to 3 hours after onset of infusion; thereafter dogs that had shown severe depression (no spontaneous activity and unresponsive to both nociceptive and non-painful stimuli) became progressively more responsive, and by the end of the infusion some dogs would stand, turn and walk spontaneously. A concomitant temporal pattern of alteration was seen for depression of the skin twitch, withdrawal reflex and miosis; these effects were maximal after two hours of infusion and thereafter diminished in magnitude. A 10 mg/kg subcutaneous test dose of morphine (17 hours (circa) after the end of infusion produeed a smaller degree of miosis and significantly less depression of the skin twitch and withdrawal reflex than this test dose did prior to infusion,

despite the fact that dogs had not completely recovered from the infused morphine, as evidenced by a subnormal pulse rate and body temperature. These findings indicated that tolerance developed during the course of infusion and was clearly demonstrable 17 hours after the end of infusion.

Administration of nalorphine (20 mg/kg) following a 7-1/2 to 8 hour infusion of morphine (3 mg/kg/hr) in the intact dog produces a syndrome which consists of marked restlessness, violent tremors, lacrimation, salivation, rhinorrhea, defecation, urination, acceleration of respiratory rate, marked tachycardia, mydriasis and a rapid increase in body temperature.

Nalorphine (20 mg/kg) produced,in the intact dog, only minimal changes, the most striking of which was miosis. Although nalorphine produced no discernible depression of the skin twitch or withdrawal reflexes in the intact dog, it produced a decided depression of the ipsilateral flexor and the crossed extensor reflexes in the spinal dog. These reflexes were even more profoundly depressed by morphine. No signs of recovery of these reflexes were observed in the spinal dog during an 8-hour infusion of morphine. In this respect, tolerance to the effect on reflex responses elicited by nociceptive stimulation in the spinal dog developed at a slower rate than did tolerance to morphine-induced alterations in reflexes evoked by nociceptive stimuli in the intact dog.

In the spinal dog, administration of nalorphine (20 mg/kg) following an 8-hour infusion of morphine (3 mg/kg/hr) evoked not only the above signs of abstinence, but in addition caused extensor hypertonus of the hindlegs, inhibited the extensor thrust reflex, increased the sensitivity for evocation of running movements in the hindlimbs and increased the magnitude of the crossed extensor and ipsilateral flexor reflexes above that observed following either nalorphine or morphine. These signs in the intact and spinal dog resemble abstinence signs observed in dogs chronically addicted to morphine and indicates that physical dependence can be consistently produced following a single infusion of morphine.

In elucidating the physiological factors responsible for signs of physical dependence, rapidly changing homeostatic levels seem to be of great importance. The cerveau isolé cat has been used to assess the effects of morphine, nalorphine, and morphine followed by nalorphine on the relationship between serum CO_2, serum pH, respiratory rate, and pulse rate. The cerveau isolé preparation has been used in this study to eliminate the effect of the hypothalamic thermoregulatory center on the respiratory mechanism.

Administration of morphine (20 mg/kg) to the feline cerveau isolé preparation depressed respiratory rate (e.g., RR 19 to 10), caused hypercapnia and increased serum pH slightly. Administration of nalorphine

(10 mg/kg) following morphine (20 mg/kg) produces a marked tachypnea (e.g., RR 10 to 35) which gradually diminishes to a modest increase in respiratory rate (2 or 3 breaths per minute over the control level), hypocapnia, and a slight but significant serum alkalosis.

The marked tachypnea observed when nalorphine was administered after morphine was accompanied by a tachycardia. These changes are part of the acute abstinence syndrome and can be explained by the fact that morphine depresses homeostatic level and creates a state in which the equilibrium-concentration of serum CO_2 is higher than in the control state. Administration of nalorphine rapidly shifts the homeostatic level back to the control level. The high serum levels of CO_2 now act as a potent stimulant to the respiratory and cardio-accelerator centers with resultant tachypnea and tachycardia.

IX. Conditioning Factors in Addiction and Habituation (Relapse)

The general theory and basic postulates around which this project was designed have been described elsewhere, and in some detail in previous annual reports. Briefly the theory states that, in part at least, relapse to addicting drugs represents a complex of responses which are conditioned to environmental stimuli (both external and internal) that were associated with periodic reduction of abstinence distress consequent to addiction. It is postulated that once physical dependence on a given drug is established, each dose of the drug serves to reinforce whatever behavior is instrumental in bringing about further administration of the drug, i.e., behavior which

results in obtaining the drug and thereby reduces objective and subjective signs of abstinence from the drug increases in probability of occurrence after each "successful" obtaining of drug as a result of the behavior. Furthermore it is postulated that the strength of such "primary" reinforcement, as well as the strength of "secondary" reinforcement by environmental stimuli regularly associated with the former, varies directly with the "effort" or "hustling" inherent in the performance of the instrumental responses. The complexity of primary and higher orders of reinforcement may be expected to greatly obscure the basis for inveterate recidivisms in man. It seemed reasonable to assume however that primary reinforcement of the sort described, as well as relatively simple secondary reinforcements, might well be used with animals to test hypotheses derived from the basic postulates.

Rats were used in previously described work, and are currently being utilized to obtain fundamental information before proceeding to use of primates. Studies are progressing on the two major and interesting aspects of the project. Pharmacological, and initial conditioning investigations of the actions of morphine and a more potent, faster acting opioid (the benzimidazole derivative known as I-G-2). The purposes of these studies are to test preference or aversive behavior to orally administered I-G-2 in nonaddicted rats, and in rats addicted by daily injections of morphine from which opioids are withheld for various periods of time; to develop valid and reliable methods of measuring tolerance to, and abstinence from

the above drugs; to determine the relative reinforcing value of ingested I-G-2 on the probability of pressing a Skinner-bar during cycles of addiction and abstinence from opioids.

In studies initiated previously it was shown that reliable evidence of physical dependence on morphine could be obtained only when the daily subcutaneous dose was maintained at 200 mg/kg. While this drug is a standard in many studies on the opioids, it is difficult to administer orally (or otherwise instrumentally) to rats, and by this route in rats lacks the fast onset of action which is essential for effective conditioning procedures. Thus in most of the conditioning and preference studies undertaken to date animals were maintained on 200 mg/kg of morphine subcutaneously daily, and consumption of I-G-2 and instrumental acts of obtaining it were used as the dependent variables. Studies completed or initiated during the year are described below.

One objective of the previous and current year was to determine whether rats could discriminate I-G-2 from water by taste (the work would be much simplified if it were shown that rats could not detect the substance over a wide range of concentrations that might be employed in subsequent investigations). In one study addicted and nonaddicted animals were deprived of water for 22 hours daily and were then permitted, through the use of appropriate "start" and "goal" cages, a choice of drinking either water or a 5-mcg/cc solution of I-G-2. Without training, neither of the groups showed preference nor aversion for either of the solutions. In a

second phase of this study distinctive cues were paired with I-G-2 and presented in the same way as above with water, in randomized right or left order. Both addicted and nonaddicted groups established a clear preference for I-G-2 with no significant differences occurring between groups as measured by amount of solution drunk. During extinction of the selective response to I-G-2, only non-significant trends were found. However in subsequent reinforcement and extinction trials in these addicted and nonaddicted rats, it was found that the addicted animals responded to short-term reinforcement, whereas the controls did not. Further studies for delineating preference and taste thresholds of I-G-2 in pressing a Skinner-bar, show that water deprived rats develop no aversion to ascending concentrations of 5, 10, 20, 30, 40, 50 or 60 mcg/cc. Thus these studies clearly indicated that I-G-2 is very appropriate for present purposes insofar as non-discrimination by taste is involved. In addition, these studies provided data showing that the effects of I-G-2 are similar to those of morphine, since the effects occurred within 4 to 9 minutes after commencement of drinking and partial evidence of cross tolerance between morphine and I-G-2. Addiction has been maintained in these rats by morphine injection (as mentioned, this is inconvenient and hazardous to animals). Studies are now started in which "direct addiction" to I-G-2 is being attempted by allowing rats free access to the liquid in their home cage instead of water. Thus far the concentrations have been 5 and 10 mcg/cc. The rats apparently maintain themselves well on these concentrations. They

show most of the signs of morphine addiction, and upon administration of nalorphine the few animals thus far tested exhibit mild abstinence signs similar to those found after morphine withdrawal. The I-G-2 concentrations will be increased to the point at which strong abstinence signs occur. Studies were also begun on instrumentation and procedures for obtaining greater validity and reliability in measuring the abstinence syndrome. This pharmacological work will consist of developing and applying apparatus for measuring precisely temperature changes, cardiac rate, oxygen consumption, and the recording of observational data during addiction and abstinence. Data thus gathered, in addition to being informative per se, will be used to determine time of peak abstinence, and thus the optimal point for use of I-G-2 as a reward or reinforcer in the behavioral studies.

Training or conditioning was an integral part of one of the above mentioned studies in which animals chose between drinking I-G-2 or water. Some indication of "relapse" to the drug was found. In another instrumental situation, addicted and control rats were conditioned to press a Skinner-bar for either I-G-2 or water under 22-hour water deprivation or 24-hour water satiation. Differential stimuli in the form of visual and tactile cues were presented with both liquids. After considerable training, reinforced bar-pressing of addicted animals exceeded that of nonaddicted rats on water-deprivation days irrespective of the liquid, whereas on water-satiation days the rates of addicted animals were significantly higher only when I-G-2 was the liquid obtained by bar-pressing. During tests in which the stabilization

dose of morphine was withheld, statistically significant intergroup differences in abstinence signs were found with peaking at the 72nd hour. In testing for "relapse," after all animals had been maintained on water only for 23 days, during which time morphine was withheld from the addicted animals, overall bar-pressing rates were found to be higher in the addicted animals. These trends appeared to be strong although not statistically significant. The latter appeared to be due to the small number of animals, several having died as a result of the morphine injections during maintained addiction.

In addition to the continuing studies mentioned, further conditioning investigations are progressing which use the Skinner-box, refined experimental design, and larger groups of both control and addicted rats. These experiments will supplement the preference and "relapse" data found previously. During the coming year a "rat-rotor" will be used by means of which different schedules of reinforcement by I-G-2 for bar-pressing can be automatically controlled. If rats can be maintained at a sufficiently high addiction level on orally administered I-G-2, the rat-rotor will be utilized for "self-addiction" purposes as well as for scheduling different periods of deprivation and integrating these with different reinforcement programs. It is anticipated that these experiments will provide information basic to the efficient initiation of studies using primates as subjects in work on conditioning factors in addiction and relapse.

X. Effect of Drug and Other Variables on "Mental Set"

This procedure, described in some detail in previous reports, may be regarded as a method for quantifying "attention." Extending this concept somewhat, the procedure as previously interpreted measures response "set" (readiness or disposition to respond). The relevance of the procedure for studying schizophrenia and for the actions of drugs on behavior depends on the findings of earlier investigators who found that certain indices of reaction time are among the most valid indicants of schizophrenia as compared with other mental illnesses. As described in previous reports, the procedure is a modification of that used by Huston and Singer (Arch. Neurol. Psychiat. 53: 365-369, 1945) for measuring auditory-manual reaction times. These are measured following visual "warning" signals at different foreperiods (the time between the warning signal and the signal to press a key) which are scheduled in "regular" and "irregular" orders. In previous years it was found that LSD-25, morphine, and pentobarbital produced changes in response set of non-psychotic postaddicts which were similar qualitatively but not quantitatively to those found in schizophrenic patients under no-drug conditions. The data on the above drugs, as well as on amphetamine, were transformed to insure homogeneity of variance, analyzed, and compared. Since that time groups of schizophrenics have been tested, and during the past year the effects of "fatigue" on set have been studied in both the addict and schizophrenic groups. The design used to isolate fatigue effects, which may influence reaction time in both groups

toward the "schizophrenic pattern," consisted of 1) comparing the first and the last 9 trials for each foreperiod series of the regular order, 2) comparing data gathered when the 2.0 second preceded the 3.5 foreperiod with data obtained when these periods were reversed, and 3) comparing reaction times found in the regular procedure when it was given first and when it was given after the irregular procedure. The data have multiplied to such an extent that analysis would be overwhelming if attempted manually. They have therefore been collated for processing by the Computing Center of the University of Kentucky (IBM-650). When the analyses are completed they will provide more clearly defined comparisons of "mental set" of schizophrenics and that of postaddicts under the above drugs, and the refined data will, at least in part, determine the extent to which the defect in set found in schizophrenia is due to alteration in the order of "warning" stimuli and to fatigue. Future work will depend in large part on the direction and significance uncovered by the computations.

ANNUAL REPORT - NARRATIVE SUMMARY

NIMH Addiction Research Center
PHS Hospital, Lexington, Kentucky

For the Period 1 January to 31 December 1960

I. General and Administrative

General. The mission of the NIMH Addiction Research Center is the conduct of research on the causes, prevention, and treatment of drug addiction. Although this may seem a narrow scientific field to many persons, it is actually a broad area. Many years of experience has shown that addiction is a very complex phenomenon with pharmacological, physiological, biochemical, socio-environmental and psychological components. The study of addiction is much more than the study of a few types of drugs. Addiction has roots in the neuroses and behavior disorders, and is therefore related to the entire field of human behavior. The work of the Addiction Research Center is pertinent not only to drug addiction specifically, but to the broad area of nervous and mental disease in general.

Thus the section on opiate addiction carries on studies of the addictiveness of new analgesics, partly, as a service function to prevent introduction of potentially addictive materials into clinical use without sufficient and proper warning. Despite the time required for this routine task, the section

was able to develop new methods for evaluating quantitatively the subjective responses following administration of opiates. The methods are simple, can be carried out by ordinary ward personnel, correlate well with the objective physical manifestations created by the drugs, and they constitute in fact a prototype technique generally applicable in clinical psychopharmacology. Simultaneously, a more sophisticated approach to evaluation of the subjective effects of drugs has been carried on by the psychological staff. Inventories have been developed which differentiate between different types of drugs and yield quantitative dose responses. Factor analyses of the data show that the information gathered in the inventory is not only useful in the evaluation of different drugs, but may also yield data of fundamental importance to the psychological modes of action of the various drugs.

The most interesting drug studied by the section on opiates during the year was a compound developed in the Hoffman-La Roche Laboratories at Basle, Switzerland -- 1-(p-Chlor-phenethyl)-2-methyl-6, 7-dimethoxy-1, 2, 3, 4-tetrahydro-isoquinoline hydrochloride (NIH-7672A, or ARC I-K-1). Adequately controlled clinical studies have shown that this drug is at least as effective as codeine in relieving pain when administered either intramuscularly or orally. Unlike other analgesics, I-K-1 does not induce clearcut morphine-like subjective effects of any intensity in former morphine addicts following administration of the highest doses that can safely be given. It is only a very weak suppressor of abstinence from morphine, being only

1/7th as potent as codeine in this respect. It does not induce a significant degree of physical dependence following administration of the highest doses compatible with safety for 30 days or more. This compound may represent the greatest dissociation between analgesia and physical addictive properties than has yet been achieved.

Experiments on the effects of drugs on the electroencephalographic and peripheral vasopressor responses to stimulation of the midbrain reticular formation, carried out by the neurophysiological section, have led to hypotheses that both "muscarinic" (blocked by atropine) and adrenergic synapses are involved in these responses. Alternative pathways may exist which take over the function of the primary pathways when either the muscarinic or adrenergic synapses are blocked. These concepts may be of fundamental importance in neurophysiology, and alternative pathways may be involved in tolerance to drugs.

The psychological unit continued work designed to elucidate psychological mechanisms involved in pain and its relief, a project obviously of great significance to clinical medicine in general. Work was initiated on probability learning in psychopaths, in the hope that light may be shed on the reasons for this puzzling pattern of behavior which is important in the areas of alcoholism and delinquency as well as in the field of opiate addiction. The psychological unit also continued work on conditioning factors of possible importance in relapse to opiate drugs.

A modest beginning was made on problems of alcohol. It consisted of elucidation and quantitation of the subjective effects of alcohol in human subjects and comparison of these with the effects of other centrally active drugs in the same patients. Also pertinent to the problem of alcohol was the project carried out in the neurophysiological section on the mechanisms of convulsions and delirium following withdrawal of barbiturates and related drugs. This study suggests that the cerebral cortex is not necessary for the development of withdrawal convulsions.

Administrative. The administrative workload of the entire Addiction Research Center has continued to grow due to the addition of more scientific personnel and to the gradual assumption of many of the functions formerly carried out by the administrative section of the hospital. Despite the increased workload, the administrative staff under the efficient leadership of Mrs. Ruth Nordstrom continued to conserve effectively the time of the scientific personnel.

The morale of the personnel within the Addiction Research Center continued at its previous high level throughout the year. Electronic engineer, John N. Schneider, left the unit in order to do his required military time in the Air Force. It is hoped he will return to us following completion of his tour of duty.

Due to Dr. Wikler's absence for a year of training, the services of a psychologist GS-5, Herbert D. Smith, were no longer required. He was replaced by a clerk-transcription machine operator GS-4, because of the

need for additional stenographic assistance within the administrative unit. Two temporary employees performed maintenance services for half of the calendar year.

Psychologist Harris E. Hill was promoted to supervising psychologist, GS-14, Harold G. Flanary to physicist GS-13, O. A. Kelly to assistant supervising aide GS-6, and C. A. Haertzen to clinical psychologist GS-11. C. W. Stivers came on duty as medical aide GS-5, and Vivian L. Jennings took the position of clerk-transcription machine operator GS-4. The position of biochemist-enzymologist GS-13 remains unfilled. A highly recommended prospect visited the unit during November, and it is hoped that he will accept the position.

Mrs. Luella R. Wainscott, library assistant, received a superior performance award, Dr. A. J. Eisenman was appointed a member of the Committee of Experts for the United Nations' program of opium research, four members of the staff were elected to the Kentucky Academy of Sciences, and Dr. H. Isbell became editor-in-chief for the United States and Canada, of Psychopharmacologia, during Dr. Wikler's absence.

Five members of the staff presented lectures on addiction and psychopharmacology at nine medical schools. The demand for teaching services is becoming so heavy that a local policy, putting some definite limitation on the amount of teaching, may have to be developed.

In addition to teaching in medical schools, Drs. C. F. Essig, A. Wikler, H. F. Fraser, W. R. Martin and H. Isbell all participated in the residency training program of the hospital. Consultative services in neurology, electroencephalography, internal medicine, and withdrawal ward management continued to be furnished to the hospital.

Dr. Harris Isbell spent the last half of his year of training (January-June 1960) in London. He visited a large number of medical schools and institutions and made many contacts with British scientists working in neuropharmacology and in psychopharmacology. He also gave several lectures to various British institutions, including university lecture on "The Pharmacology of Opiate Addiction," Kings College, University of London, and the Eighth Kelynack Memorial Lecture, on "Perspectives in Research on Opiate Addiction," before the British Society for the Study of Addiction.

Dr. Abraham Wikler left for Europe the latter part of June for a year of study and training. He has had a very successful half-year and has visited many laboratories in Switzerland, Scandinavia, and the low countries. He delivered, by invitation, a lecture on "Survey of Research on Alcohol at the Addiction Research Center" at the 26th International Congress on Alcoholism, in Stockholm, Sweden, 31 July 1960. He has, in addition, delivered lectures at various universities and institutions in Great Britain.

The most pressing physical need of the Addiction Research Center is about to be met -- an appropriation of $350,000 was approved by the Congress for construction of a basic research building. Preliminary plans for the building and the site have now been approved by NIMH and the Division of Hospitals, and it is hoped that architectural contract will soon be let and detailed planning completed in time to break ground for the building in March or April 1961.

II. Studies on Addictive Properties of New Analgesics

These studies are designed primarily for the purpose of providing information on the human addiction liabilities of new drugs (chiefly potent analgesics) with morphine-like properties for use by authorities responsible for recommending measures for control of such agents at national and international levels. They also assist the medical profession in evaluation of the therapeutic and toxic properties of new drugs in clinical use, and provide opportunities for basic research on the mechanisms of tolerance, addiction, and habituation.

During the current year improvements were made in methodology for measuring the overall abuse-liability of new drugs. Thus "subjective" and "objective" rating scales of behavioral change (with particular reference to "euphoria") were tested for several new drugs under double-blind conditions. As noted in the last annual report, these quantitative data revealed a high degree of concordance between the ratings of our experimental subjects ("subjective") and the ratings of the observers ("objective") in the case of

the potent analgesics such as morphine and heroin, but considerable discordance when weaker analgesics were tested. The addictive "ratings" of opiate addicts for a series of morphine-like drugs, respecting the parameters (1) identification as "dope" (opiate), (2) "strength" (potency), and (3) the extent to which they "would like to take each drug daily" covaried with the intensity of the abstinence syndrome which developed when each of these drugs was discontinued abruptly. The degree of "acceptance" of drugs by addicts was significantly influenced by the route of administration; for example, positive "acceptance" of morphine orally was zero, 40 per cent when given subcutaneously, and 54 per cent by the intravenous route. Heroin had an "acceptance" rating of 32 per cent subcutaneously as compared to 76 per cent intravenously.

Since addicts in the United States prefer to take their drugs intravenously, an intensive comparison was made of intravenous morphine and heroin, using single doses and four levels of each drug in order to obtain the relative potency of each. In addition, both morphine and heroin were administered intravenously to postaddicts in an 18-day direct addiction test. All studies utilized a "cross-over," "double-blind" design. Using a variety of objective and subjective measures, it was found that 1 mg of heroin was equivalent to 1.80 to 2.66 mg of morphine sulfate. Postaddicts could identify morphine and heroin as such with a high degree of accuracy when these

agents were administered intravenously, either acutely or chronically. Though they showed no preference for a single injection of one or the other of these drugs, they expressed a preference for heroin in the short-term addiction study (76 per cent positive "acceptance" for heroin, and 54 per cent for morphine).

Addictiveness of seven new synthetic analgesic compounds. In the text, Addiction Research Center numbers (ARC) or generic names will be used to designate compounds.

1. 1-(p-Chlor-phenethyl)-2-methyl-6, 7-dimethoxy-1, 2, 3, 4-tetrahydro-isoquinoline HCl (NIH-7672A, ARC I-K-1)

This is a new isoquinoline derivative reported to have analgesic potency in man comparable to that of codeine, but tests in postaddicts show its addictiveness is less than that of codeine, and even less than that of d-propoxyphene. This means that it shows a favorable dissociation between analgesic and addictiveness. Clinically it would probably be satisfactory only for oral use because it is very insoluble and a potent tissue irritant when injected, a feature which greatly reduces its abuse liability.

When given orally to former addicts, I-K-1 did not induce euphoria nor suppress abstinence in morphine dependent patients, nor did it induce any detectable degree of physical dependence when administered on an addictive schedule for 60 days. Although it partially suppressed abstinence when given intramuscularly, it was only about 1/7th as potent as codeine in this respect, and such large doses of an acid solution were required that

protracted inflammation at the site of injection ensued. In single intravenous doses of 60 and 120 mg it induced subjective effects somewhat similar to those of comparable doses of codeine, but it was not feasible to administer intravenous doses repeatedly because of chemical thrombosis of the veins; hence any danger of addictiveness by the intravenous route is minimal. Work on I-K-1 has been completed and will be reported to the Committee on Drug Addiction and Narcotics of the National Research Council, and prepared for publication.

2. 2-(Beta-hydroxyphenethylamino)-pyridine . Hcl (Phenyramidol, ARC I-L-1, and
3. N-Isopropyl-2-methyl-2-propyl-1, 3-propanediol dicarbamate (Carisoprodol, ARC I-M-1)

Phenyramidol and carisoprodol will be described together. They were investigated because both were alleged to be internuncial neuronal blockers and both compounds were being marketed as orally effective muscle relaxants with analgesic properties.

Phenyramidol showed no evidence of addictive properties.

Carisoprodol, in large single doses, induced barbiturate-like effects; it partially but significantly suppressed abstinence in doses of 15 to 20 times the dose of morphine; and, although tolerance to sedative effects developed in the direct addiction tests, it was not identified as an opiate by former morphine addicts and there was no abstinence syndrome when the drug was discontinued abruptly. Carisoprodol has less addictiveness than codeine and d-propoxyphene.

Work on phenyramidol and carisoprodol is complete and will be reported to the Committee on Drug Addiction and Narcotics, NRC.

4. Alpha-dl-3-acetoxy-4, 4-diphenyl-6-methylaminoheptane hydrochloride (NIH-7667, ARC I-C-25)

This is a derivative of methadone. Subcutaneously it is more potent than morphine in inducing morphine-like euphoria and in suppressing abstinence from morphine. A report to this effect will be made to the Committee on Drug Addiction and Narcotics, NRC.

5. 6-Acetyl-3 ethoxydihydromorphine (NIH-7623, ARC I-A-38)

This compound is related structurally to both morphine and heroin. Subcutaneous doses of 100 to 200 mg induced consistent morphine-like effects and it was about one-half as effective as morphine in suppressing abstinence. It is considered to have abuse liability greater than that of codeine but possibly less than that of morphine. A report to this effect will be made to the Committee on Drug Addiction and Narcotics, NRC.

6. N-(1-Methyl-2-piperidinoethyl)-propioanilide . Hcl (NIH-7602, ARC I-I-1, Phenampromid), and
7. N-(2[Methyl)-phenethylamino]-propyl)-propioanilide (NIH-7603, ARC I-J-1, Diampromid)

Phenampromid or diampromid administered orally induced morphine-like subjective effects and behavior in nontolerant former morphine addicts, and both suppressed symptoms of abstinence from morphine.

A report on phenampromid and diampromid was made to the Committee on Drug Addiction and Narcotics, NRC, in January 1960. The Committee advised the Commissioner of Narcotics that both compounds should be placed under control of the narcotic laws of the United States. The President, after appropriate action by the Commissioner, promulgated an order to this effect in October 1960.

III. Acute and Chronic Intoxication with Drugs Other than Analgesics, Barbiturates or Alcohol.

1. Cross tolerance between LSD and psilocybin.

Two experiments were completed during the year. In the first, 10 subjects received LSD in doses increasing to 1.5 mcg/kg over a 6-day period, and on another occasion the same patients received psilocybin in doses increasing to 150 mcg/kg over the same period of time. The patients were then tested with the drug they had been receiving, and "challenged" with the drug they had not been receiving. In the second experiment, 9 patients received LSD in doses increasing to 1.5 mcg/kg over a period of 12 days, and on another occasion, psilocybin in doses increasing to 210 mcg/kg over a period of 12 days, following which they were tested with the drug they had been receiving and "challenged" with the converse drug. The second experiment was carried out to determine if administration of psilocybin over a longer period of time would result in a higher degree of cross tolerance to LSD. The results in both experiments were similar. Definite tolerance to psilocybin developed in both experiments, as manifested by the reduction in

both "objective" and "subjective" parameters of response. The patients tolerant to psilocybin also showed a reduced response to LSD. Conversely patients tolerant to LSD also showed a reduced response to psilocybin. Direct tolerance to LSD was greater in degree than direct tolerance to psilocybin. Increasing the dose and length of time over which psilocybin was administered did not increase the degree of tolerance and cross tolerance. This demonstration of cross tolerance between the two drugs reinforces the hypothesis, which was based on the similarity of the clinical patterns of effects induced by both, that they induce psychic aberrations by acting through common mechanisms or through mechanisms serving a final common pathway. The study suggests that psychotomimetic drugs can be classified into definite groups by studying tolerance and cross tolerance.

2. Cross tolerance between LSD and mescaline.

As the initial step in this project, a comparison has been made of the objective and subjective effects of LSD and mescaline in 10 patients. Patterns of effects induced by both drugs were very similar. Objective findings after both included elevation of temperature, elevation of blood pressure, diminution in threshold for the kneejerk, and pupillary dilatation. Subjective reports after both drugs included anxiety, feeling of unreality, perceptual distortion (particularly visual), and hallucinations. LSD is approximately three-thousand times as potent as mescaline. Cross-tolerance experiments between both drugs will be completed early in 1961.

3. Psilocin.

This compound is simply dephosphorylated psilocybin. Its effects, in comparison with those of mescaline and LSD, were studied in 10 men. In the doses and manner used, it proved to be the most reliable psychotomimetic drug we have ever studied. All 10 patients who received 150 mcg/kg of psilocin intramuscularly developed marked symptoms of depersonalization, vivid visual hallucinations, and many of them lost insight. Onset of action of psilocin is extremely rapid and the effects are largely dissipated in less than four hours. Because of its short length of action, psilocin may be preferable to LSD or mescaline as a psychotherapeutic tool or as a possible psychodiagnostic agent.

IV. Clinical Studies of Intoxication with Alcohol, Barbiturates, and Related Drugs.

During the year work progressed on the psychopathology of alcoholism as compared with that of narcotic addiction, on acute effects of alcohol and barbiturates on verbal report, and on testing for possible correlations between such drug effects and personality characteristics. Previously reported were findings on the first application of factor analysis to personality profiles (MMPI) of three institutionalized groups, 200 alcoholics, 200 narcotic addicts, and 200 criminals. This analysis indicated considerable similarity of these populations, especially with regard to psychopathic traits. During the present year an inverted, rectangular factor analysis was applied, using all profiles to check and refine previous results. From

these analyses emerged five factors similar to those found earlier but more clearly defined. The first and common factor, on which practically all profiles regardless of group were heavily loaded, was interpreted as social deviance. The characteristic was so strong in the three populations that no factor independent of such psychopathic traits was found. In Factors 2, 3, 4 and 5 the dominating influence of social deviance was combined with various neurotic and schizoid tendencies, none of which however were sufficiently differentiating to even approach diagnostic significance. This study, for which early publication is planned, strongly suggests that psychopathy or social deviance is of specific etiological significance to neither alcoholism nor narcotic addiction, nor is it of such significance for the addictions in general. However it does appear that such measures as were used in the study are general predictors of asocial or antisocial actions, including addictions of various sorts. Predictors of the specific directions of such behavior apparently must be sought elsewhere, perhaps they may still be sought partially within the framework of social deviance, with emphasis on the level of availability of deviant modes of action and on the lack or impairment of behavioral controls which result in such deviancy.

Measurement of subjective effects of three doses of alcohol and one of pentobarbital in acute studies were continued, using the Addiction Research Center Inventory (ARCI). Previous pilot work had established a dose of pentobarbital, and initial and maintaining doses of alcohol which produced appropriate intoxication for a period of about three hours. During the year,

gathering of data on the main study was completed. The data were analyzed in the same manner as those discussed under Psychological Studies of Addiction (see VII below). Two scales of discriminating items were developed for both alcohol and pentobarbital (3.00 cc/kg of 30% alcohol with maintaining doses, and 200 mg of pentobarbital). Publication of the studies as separates and in manual form is anticipated. Work is also going forward, by means of correlational and other techniques, to ascertain common and specific effects of these drugs within the limits of the ARCI. Administration of the Guilford-Zimmerman Temperament Survey to post-addicts, under conditions of no-drug and the above dose of alcohol, failed to support Eysenck's theory concerning the actions of alcohol on individuals showing different degrees of introversion-extroversion. Significant correlations were found on four scales of this survey. They indicate that the emotionally labile, depressed individual is most strongly affected by alcohol. These data are to be reanalyzed before being prepared for publication. Other personality-drug effect correlations will be implemented as ARCI data are collated with those from the MMPI.

V. Biochemistry of Addiction

Excretion of heroin and codeine.

Since the toxicology laboratory of the University of Wisconsin and this laboratory encounter some of the same problems concerning the routine analyses of urines of suspected addicts for the detection of opium alkaloids and related drugs, it was thought that a joint study would be mutually beneficial. The purpose of the study was to determine just how long and how much morphine could be detected in the urine of subjects possessing high and low tolerance to heroin after abrupt withdrawal of the drug, and how much and how long morphine, codeine, and other codeine metabolites could be detected in the urine of subjects possessing high and low tolerance to codeine. Extraction and chromatography methods devised by Dr. G. J. Mannering were used for the study.

The unexpected finding that nicotine has the same R_f as morphine in the chromatography solvent system used for the heroin experiment necessitated a change in the proposed procedure for the quantitative assay of the chromatograms for morphine. Much time was spent in developing a method that excluded nicotine. A method of eluting the chromatograms and reacting with silicomolybdic acid which gave suitable recoveries, without interference from nicotine, was eventually devised. Our half of the duplicate samples from the heroin study have been quantitated, however, the results are not reported herein since Dr. Mannering has not completed his samples. The

codeine phase of the experiment has been completed through the initial extraction procedure, and will be finished when Dr. Mannering decides on the best procedure to follow for the final quantitation of the residues.

Opiate and synthetic drugs excreted in urines submitted by the clinical service.

The introduction of routine chromatography in the tests for urinary morphine has resulted in tests which are free of interference from newly introduced drugs. Urinary demerol has been separated by chromatography into demerol and nor-demerol.

VI. Neurophysiology and Neuropharmacology of Chronic Intoxication of Barbiturates and Related Drugs

Elevation of electrical seizure thresholds.

Daily induction of convulsions by slowly increasing the voltage of the stimulating electrical currents until a fit ensues results in a progressive increase in the voltage necessary for production of a convulsion ("ECT" tolerance). Such tolerance occurred in adrenalectomized animals maintained on fixed amounts of adrenal corticosteroids and therefore is not likely due to increased adrenal cortical activity arising from the stress of repeated convulsions. If one pair of stimulating electrodes are implanted anteriorly and another pair posteriorly, daily stimulation of the anterior pair results in increase of the threshold through the posterior pair, even though stimulation is applied to the posterior pair at intervals widely separated in time. This suggests a general cerebral change rather than a focal change directly beneath the stimulating electrodes.

The project is to be continued. If elevation of the ECT threshold can be induced in rats by daily stimulation through corneal electrodes, the rate of progress can be accelerated. It will become possible to determine whether daily electrostimulation results in an increased production of a hypothetical chemical by the brain which is a "natural" anticonvulsant.

Effects of bilateral decortication on barbiturate withdrawal convulsions.

Three totally decorticated dogs and one decorticated cat did not have grand mal seizures following abrupt withdrawal of barbiturates after long intoxication, whereas all unoperated controls did have convulsions. Thus it seems that the cerebral cortex is necessary for grand mal seizures during withdrawal of barbiturates. Pentylenetetrazole (metrazole) induced typical grand mal convulsions in a totally decorticated dog. Determinations of the amounts of pentylenetetrazole required for the induction of convulsions in decorticated dogs and their controls should be necessary before a clear interpretation can be made.

These investigations are to be continued, using higher dose levels of barbiturates and longer periods of chronic intoxication. In addition, electrical recordings from subcortical structures will be made in order to determine whether barbiturate withdrawal seizures originate in subcortical structures. In the latter case, the effect of decortication might be due to simple elevation in the threshold for grand mal convulsions.

Effect of dilantin on barbiturate withdrawal convulsions.

Maximum tolerated doses of dilantin orally, intraperitoneally and intravenously did not prevent convulsions due to abstinence from barbiturates in chronically intoxicated dogs. Further pharmacological analysis of the mechanisms of barbiturate withdrawal convulsions will be carried out, using such drugs as scopolamine, physostigmine, and sodium hydrazide.

Effect of unilateral cerebral cortical lesions on the occurrence of convulsions during withdrawal of barbiturates from small dogs.

Barbiturate withdrawal convulsions did not occur in any of 4 animals in which focal cerebral cortical lesions were induced by injection of either aluminum hydroxide cream or by freezing with ethyl chloride. Convulsions did occur in the controls. The project is to be continued utilizing higher doses of barbiturates, other species of animals such as rats and monkeys, the effect of topically applied acetylcholine during withdrawal of barbiturates, and the thresholds for direct cortical responses to electrical stimulation during abstinence from barbiturates.

VII. Psychological Studies of Addiction

Gathering and analysis of data on the Addiction Research Inventory for differentiating subjective effects of drugs continued to be the main clinical study of drug actions in psychology. This work has been progressing for several years through construction of a 550-item inventory from an original pool of 3400 questions (by means of exploratory work on this pool with various drugs) to development of various drug scales. The final form of the inventory was printed and administered to approximately 175 postaddict subjects under the following conditions: no-drug, placebo, morphine, alcohol (4 dose levels), pentobarbital, chlorpromazine, LSD-25 (2 dose levels), amphetamine, and pyrahexyl compound (2 dose levels). All individuals were also given two different personality inventories and a test of literacy and intelligence. During 1960, gathering of data was completed. The data from subjects who produced valid tests, as indicated by a rational scale of consistency, were transcribed to punchcards and processed in various ways by the Computing Center of the University of Kentucky.

By means of an item analysis all other conditions were compared with placebo on a first group of 50 subjects. This method uses the frequencies of "true" and "false" responses, and a technique for determining statistical significance to isolate all items of the inventory which discriminate separately between placebo and every other condition at or beyond the 0.05 percent level. These procedures resulted in initial scales of differentiating items or questions. Similar data on a second group of 50 subjects were

processed in the same manner. Items were then chosen for the final scales which maintained discrimination in both groups at less than the 0.05-per cent level of significance. These final scales were then tested on a third group of 30 subjects for purposes of validity generalization. Scales derived in this way were termed "primary," since they were composed of items showing the strongest drug effects. In addition, "secondary" scales were developed concurrently with the above. These scales consisted of items selected in the placebo and the other conditions in the same manner, but that differentiated placebo and the other conditions in the total at the 0.05-level of significance. Although only superficial analysis of scale content has been made, the primary scales appear to be heavily loaded with sensory and affective or mood changes, and alteration in the stimulation-depression continuum. The secondary scales are composed of items which appear not to be as physiologically-based. However in the case of LSD-25, the only drug to which factor analysis has been applied, it was found that apparently all "secondary" effects are dependent upon the occurrence of the "primary" effects. Such inter-relationships are to be investigated in the other drug conditions. Separate publication is anticipated for each of the developed drug scales. These initial publications and the preparation of a test manual, however, cannot include detailed analyses of the actions of each drug and their inter-relationships. Such analyses of common, multiple, and specific drug actions have been started, but they are so complex and refractory to statistical techniques that they must be dealt with as individual

studies. Factor analysis is by no means ideal for most of the work, and development of original methods may be a necessity. The work of discovering possible correlations between drug-effects and personality characteristics is also one of the main objectives of these investigations. Preliminary work is encouraging, but sustained effort must await completion of several other phases in this area. As time and personnel permit, the ARC Inventory will be standardized on normal populations with and without drug medication. It will be used for investigating alcoholism and schizophrenia, and should be especially useful in measuring psychopathy or social deviance.

Other studies on human subjects continued during the year included the gathering of Minnesota Multiphasic Personality Inventory profiles on physician addicts, and investigations of probability learning in former addicts. Both have progressed rather slowly but for different reasons. Previously, addict physicians were tested 30 days or more after their admission to the hospital. For some unknown reason, the number of available subjects was not maintained at the rate found in the earlier part of the study. Testing at 10 days after admission during the past year was instituted to facilitate gathering of an adequate sample, and to compare such profiles with those obtained after 30 days. The study is being continued for the next year, but prospects are not encouraging because of the current low admission rate.

The probability learning study, which is now in progress, is one of a number of different procedures which will be directed toward comparing variables which control decision making and thus behavior in the "psychopath" and normal subject. Is the behavior of the psychopath controlled to a greater extent by immediate rather than remote contingencies, by negative rather than positive reinforcements, and more nearly by immediate personal gratification and relief from frustrations than is the behavior of the "normal" individual? As appropriate procedures are developed for answering these questions, drug produced alterations in the controlling variables will be introduced. During 1960 data were gathered on 60 subjects, using a probability learning procedure. This study was postponed to allow collection of data on the ARC Inventory, and the addition of several more groups is necessary to draw more than tentative conclusions. The procedure involves an estimate or prediction of future events in a simple situation where one of three lights will be lit. The task of the subject is to predict which light will be lit on successive trials. His only source of information is his experience in the situation. He does not know that the separate lights are presented 70, 20, and 10 per cent of the trials in randomized order. Data accumulated to date indicate that addicts overestimate the most frequent alternative and underestimate the least frequent. Thus far this finding is the opposite to that found in normals. Also such "choice" behavior in the addict is altered in the direction of "normalcy" by administration of appropriate doses of morphine. Various other types of reinforcement will be used under control and drug conditions.

In rats, the practical and theoretical aspects of anxiety reduction by potent analgesic drugs were pursued further. This series of studies was originally begun on human subjects to test the hypothesis that reduction of pain-conditioned anxiety is a necessary action of potent analgesics, and to develop a method for detecting such drugs. A very promising procedure was devised and published. The theoretical basis for the study was strongly supported. Continued work with this procedure in man was not feasible since it was very penalizing to the subjects and to the experimenter as well, because it was necessary that he test the apparatus on himself. An animal method was then set up which complemented the human work and involved the same general principles. Rats were trained to press a lever in a Skinner-box to obtain food. A 4-minute tone terminated by a brief, strong electric shock was applied to the feet of the rat during each daily session. Shortly, the tone acquired an inhibiting function, producing cessation of lever-pressing for its duration. This inhibition was assumed to represent the effects of pain-conditioned anxiety or a conditioned emotional response (CER). It was then hypothesized that potent analgesics would reduce this form of inhibition, as had occurred in man, and that other classes of drugs would not. Work on this technique, which extended over several years and which is being continued in modified form, was completed on 10 drugs in multiple doses. It was found that opioids produced significant dose-effect curves of CER reduction; optimal doses practically eliminated effects of the tone. Significant dose-effect curves were found for no other drug except

pentobarbital and then only at 20 minutes after injection. Effects of drugs other than these two classes are to some extent dependent upon the intensity of the tone and other parameters. Publication of several papers on this CER work is being postponed until ancillary studies clarify further the actions of pertinent drugs on auditory discrimination, sufficient work on other supplementary procedures having already been completed. In this work the most encouraging procedure is the imposition of a tone discrimination upon an escape response. Apparently this type of conditioning has never been accomplished previously. Shock intensity is extremely critical. The rat runs from an electrified start box, down a short alley to escape in one of two end boxes. Tone is in one end box, signalling the "hot," or non-escape side. Apparently no discrimination involving choice can be established when the shock is at such a level as to be a prepotent stimulus. In the limited number of animals that have thus far been successfully conditioned in this way, when using optimal doses found in the CER work, morphine and pentobarbital abolish avoidance behavior, raise the "escape" shock level, but have no effect on discriminative escape, while amphetamine has an effect on only the latter, disrupting it. These studies of the CER and ancillary investigations may be of considerable practical and theoretical value in several different areas other than pain and analgesia.

Interoceptive conditioning has been studied little in the United States and such endeavors have been sporadic. It would appear that at least some behavioral effects of drugs can be reasonably subsumed under such learning or conditioning principles. Work on the actions of drugs at the ARC assumes that one mechanism by which drugs produce effects on behavior is through alteration of internal stimuli. Such changes may produce effects in behavior by facilitating or inhibiting responses directly, or drug-produced changes in the organism may come to act as occasions for responses in their own right, i.e., become stimuli to which responses are conditioned (The studies to be described later, on a pharmacodynamic theory of relapse to narcotic drugs, are partially based upon such reasoning). Previous annual reports summarized studies on rats in which support for such a position was obtained and in which amphetamine was found to act as a "depressant" rather than a stimulant. Initial work in rats on the effects of autonomic blocking agents was also described. Studies on the latter are being continued. The hypothesis being tested is that while autonomic effector activity is not essential for the acquisition of a traumatic avoidance response, such activity serves to increase resistance of the response to extinction. To test this hypothesis, acquisition and extinction of a traumatic avoidance response under non-medicated conditions are compared with these procedures under the ganglionic blocking agent Ecolid. Because there is hazard in assuming that drugs always act according to published descriptions, it was necessary to demonstrate initially that Ecolid is an autonomic blocking

drug. After several tedious and discouraging pilot studies, partially shown in the previous report, a procedure was found which demonstrated that Ecolid does significantly reduce blood pressure in the otherwise unmedicated rat. To our knowledge this is the first demonstration of such effects. A method was then devised for producing traumatic avoidance conditioning. As yet the experimental design has not been completed, about half of the groups remain to be tested. However, the data show (contrary to expectation) that Ecolid slightly impairs conditioning to asymptotic performance, but does indeed hasten markedly the extinction or "dropping-out" of the traumatic response. As shown in other studies, shock intensity during conditioning is an important parameter in determining the strength of the conditioned response as measured by resistance to extinction. In this study the least effect of the drug was found on extinction after conditioning on the highest of three shock levels. This work is being continued. Investigations of this nature may have significance for predicting and therapeutically controlling emotion and some forms of mental illness.

VIII. The Mode of Action of Central Nervous System Depressants

During the last year work on the mode of action of drugs on brainstem integrating and regulatory mechanisms has been limited to investigations of acute tolerance and physical dependence on opiates in the dog and cat. Various aspects of these problems have been studied in the intact dog, the spinal dog, and the *cerveau isolé* cat.

In addition to evaluating the effect of morphine and nalorphine on behavioral states in intact and spinal dogs (e.g., sleep, sedation, restlessness, etc.), observations have been made on pulse rate, respiratory rate, body temperature, pupillary diameter, skin twitch, and withdrawal reflexes (intact dog), patellar reflex (S. D. - spinal dog), ipsilateral flexor reflex (S. D.), contralateral crossed extensor reflex (S. D.), and the extensor thrust reflex (S. D.). The effects of single subcutaneous doses of morphine sulfate (10 mg/kg) and nalorphine HC_1 (20 mg/kg) were evaluated for a 5-hour period following injection to provide a base line for the determination of tolerance and to evaluate morphine-nalorphine interactions in both intact and spinal dogs.

Morphine sulfate was infused at a rate of 3 mg/kg/hr in intact dogs for 7-1/2 to 8 hours. Maximum sedation was observed 2 to 3 hours after onset of infusion; thereafter dogs that had shown severe depression (no spontaneous activity and unresponsive to both nociceptive and non-painful stimuli) became progressively more responsive, and by the end of the infusion some dogs would stand, turn and walk spontaneously. A concomitant temporal pattern of alteration was seen for depression of the skin twitch, withdrawal reflex and miosis; these effects were maximal after two hours of infusion and thereafter diminished in magnitude. A 10 mg/kg subcutaneous test dose of morphine (17 hours (circa) after the end of infusion produeed a smaller degree of miosis and significantly less depression of the skin twitch and withdrawal reflex than this test dose did prior to infusion,

despite the fact that dogs had not completely recovered from the infused morphine, as evidenced by a subnormal pulse rate and body temperature. These findings indicated that tolerance developed during the course of infusion and was clearly demonstrable 17 hours after the end of infusion.

Administration of nalorphine (20 mg/kg) following a 7-1/2 to 8 hour infusion of morphine (3 mg/kg/hr) in the intact dog produces a syndrome which consists of marked restlessness, violent tremors, lacrimation, salivation, rhinorrhea, defecation, urination, acceleration of respiratory rate, marked tachycardia, mydriasis and a rapid increase in body temperature.

Nalorphine (20 mg/kg) produced,in the intact dog, only minimal changes, the most striking of which was miosis. Although nalorphine produced no discernible depression of the skin twitch or withdrawal reflexes in the intact dog, it produced a decided depression of the ipsilateral flexor and the crossed extensor reflexes in the spinal dog. These reflexes were even more profoundly depressed by morphine. No signs of recovery of these reflexes were observed in the spinal dog during an 8-hour infusion of morphine. In this respect, tolerance to the effect on reflex responses elicited by nociceptive stimulation in the spinal dog developed at a slower rate than did tolerance to morphine-induced alterations in reflexes evoked by nociceptive stimuli in the intact dog.

In the spinal dog, administration of nalorphine (20 mg/kg) following an 8-hour infusion of morphine (3 mg/kg/hr) evoked not only the above signs of abstinence, but in addition caused extensor hypertonus of the hindlegs, inhibited the extensor thrust reflex, increased the sensitivity for evocation of running movements in the hindlimbs and increased the magnitude of the crossed extensor and ipsilateral flexor reflexes above that observed following either nalorphine or morphine. These signs in the intact and spinal dog resemble abstinence signs observed in dogs chronically addicted to morphine and indicates that physical dependence can be consistently produced following a single infusion of morphine.

In elucidating the physiological factors responsible for signs of physical dependence, rapidly changing homeostatic levels seem to be of great importance. The cerveau isolé cat has been used to assess the effects of morphine, nalorphine, and morphine followed by nalorphine on the relationship between serum CO_2, serum pH, respiratory rate, and pulse rate. The cerveau isolé preparation has been used in this study to eliminate the effect of the hypothalamic thermoregulatory center on the respiratory mechanism.

Administration of morphine (20 mg/kg) to the feline cerveau isolé preparation depressed respiratory rate (e.g., RR 19 to 10), caused hypercapnia and increased serum pH slightly. Administration of nalorphine

(10 mg/kg) following morphine (20 mg/kg) produces a marked tachypnea (e.g., RR 10 to 35) which gradually diminishes to a modest increase in respiratory rate (2 or 3 breaths per minute over the control level), hypocapnia, and a slight but significant serum alkalosis.

The marked tachypnea observed when nalorphine was administered after morphine was accompanied by a tachycardia. These changes are part of the acute abstinence syndrome and can be explained by the fact that morphine depresses homeostatic level and creates a state in which the equilibrium-concentration of serum CO_2 is higher than in the control state. Administration of nalorphine rapidly shifts the homeostatic level back to the control level. The high serum levels of CO_2 now act as a potent stimulant to the respiratory and cardio-accelerator centers with resultant tachypnea and tachycardia.

IX. Conditioning Factors in Addiction and Habituation (Relapse)

The general theory and basic postulates around which this project was designed have been described elsewhere, and in some detail in previous annual reports. Briefly the theory states that, in part at least, relapse to addicting drugs represents a complex of responses which are conditioned to environmental stimuli (both external and internal) that were associated with periodic reduction of abstinence distress consequent to addiction. It is postulated that once physical dependence on a given drug is established, each dose of the drug serves to reinforce whatever behavior is instrumental in bringing about further administration of the drug, i.e., behavior which

results in obtaining the drug and thereby reduces objective and subjective signs of abstinence from the drug increases in probability of occurrence after each "successful" obtaining of drug as a result of the behavior. Furthermore it is postulated that the strength of such "primary" reinforcement, as well as the strength of "secondary" reinforcement by environmental stimuli regularly associated with the former, varies directly with the "effort" or "hustling" inherent in the performance of the instrumental responses. The complexity of primary and higher orders of reinforcement may be expected to greatly obscure the basis for inveterate recidivisms in man. It seemed reasonable to assume however that primary reinforcement of the sort described, as well as relatively simple secondary reinforcements, might well be used with animals to test hypotheses derived from the basic postulates.

Rats were used in previously described work, and are currently being utilized to obtain fundamental information before proceeding to use of primates. Studies are progressing on the two major and interesting aspects of the project. Pharmacological, and initial conditioning investigations of the actions of morphine and a more potent, faster acting opioid (the benzimidazole derivative known as I-G-2). The purposes of these studies are to test preference or aversive behavior to orally administered I-G-2 in nonaddicted rats, and in rats addicted by daily injections of morphine from which opioids are withheld for various periods of time; to develop valid and reliable methods of measuring tolerance to, and abstinence from

the above drugs; to determine the relative reinforcing value of ingested I-G-2 on the probability of pressing a Skinner-bar during cycles of addiction and abstinence from opioids.

In studies initiated previously it was shown that reliable evidence of physical dependence on morphine could be obtained only when the daily subcutaneous dose was maintained at 200 mg/kg. While this drug is a standard in many studies on the opioids, it is difficult to administer orally (or otherwise instrumentally) to rats, and by this route in rats lacks the fast onset of action which is essential for effective conditioning procedures. Thus in most of the conditioning and preference studies undertaken to date animals were maintained on 200 mg/kg of morphine subcutaneously daily, and consumption of I-G-2 and instrumental acts of obtaining it were used as the dependent variables. Studies completed or initiated during the year are described below.

One objective of the previous and current year was to determine whether rats could discriminate I-G-2 from water by taste (the work would be much simplified if it were shown that rats could not detect the substance over a wide range of concentrations that might be employed in subsequent investigations). In one study addicted and nonaddicted animals were deprived of water for 22 hours daily and were then permitted, through the use of appropriate "start" and "goal" cages, a choice of drinking either water or a 5-mcg/cc solution of I-G-2. Without training, neither of the groups showed preference nor aversion for either of the solutions. In a

second phase of this study distinctive cues were paired with I-G-2 and presented in the same way as above with water, in randomized right or left order. Both addicted and nonaddicted groups established a clear preference for I-G-2 with no significant differences occurring between groups as measured by amount of solution drunk. During extinction of the selective response to I-G-2, only non-significant trends were found. However in subsequent reinforcement and extinction trials in these addicted and nonaddicted rats, it was found that the addicted animals responded to short-term reinforcement, whereas the controls did not. Further studies for delineating preference and taste thresholds of I-G-2 in pressing a Skinner-bar, show that water deprived rats develop no aversion to ascending concentrations of 5, 10, 20, 30, 40, 50 or 60 mcg/cc. Thus these studies clearly indicated that I-G-2 is very appropriate for present purposes insofar as non-discrimination by taste is involved. In addition, these studies provided data showing that the effects of I-G-2 are similar to those of morphine, since the effects occurred within 4 to 9 minutes after commencement of drinking and partial evidence of cross tolerance between morphine and I-G-2. Addiction has been maintained in these rats by morphine injection (as mentioned, this is inconvenient and hazardous to animals). Studies are now started in which "direct addiction" to I-G-2 is being attempted by allowing rats free access to the liquid in their home cage instead of water. Thus far the concentrations have been 5 and 10 mcg/cc. The rats apparently maintain themselves well on these concentrations. They

show most of the signs of morphine addiction, and upon administration of nalorphine the few animals thus far tested exhibit mild abstinence signs similar to those found after morphine withdrawal. The I-G-2 concentrations will be increased to the point at which strong abstinence signs occur. Studies were also begun on instrumentation and procedures for obtaining greater validity and reliability in measuring the abstinence syndrome. This pharmacological work will consist of developing and applying apparatus for measuring precisely temperature changes, cardiac rate, oxygen consumption, and the recording of observational data during addiction and abstinence. Data thus gathered, in addition to being informative per se, will be used to determine time of peak abstinence, and thus the optimal point for use of I-G-2 as a reward or reinforcer in the behavioral studies.

Training or conditioning was an integral part of one of the above mentioned studies in which animals chose between drinking I-G-2 or water. Some indication of "relapse" to the drug was found. In another instrumental situation, addicted and control rats were conditioned to press a Skinner-bar for either I-G-2 or water under 22-hour water deprivation or 24-hour water satiation. Differential stimuli in the form of visual and tactile cues were presented with both liquids. After considerable training, reinforced bar-pressing of addicted animals exceeded that of nonaddicted rats on water-deprivation days irrespective of the liquid, whereas on water-satiation days the rates of addicted animals were significantly higher only when I-G-2 was the liquid obtained by bar-pressing. During tests in which the stabilization

dose of morphine was withheld, statistically significant intergroup differences in abstinence signs were found with peaking at the 72nd hour. In testing for "relapse," after all animals had been maintained on water only for 23 days, during which time morphine was withheld from the addicted animals, overall bar-pressing rates were found to be higher in the addicted animals. These trends appeared to be strong although not statistically significant. The latter appeared to be due to the small number of animals, several having died as a result of the morphine injections during maintained addiction.

In addition to the continuing studies mentioned, further conditioning investigations are progressing which use the Skinner-box, refined experimental design, and larger groups of both control and addicted rats. These experiments will supplement the preference and "relapse" data found previously. During the coming year a "rat-rotor" will be used by means of which different schedules of reinforcement by I-G-2 for bar-pressing can be automatically controlled. If rats can be maintained at a sufficiently high addiction level on orally administered I-G-2, the rat-rotor will be utilized for "self-addiction" purposes as well as for scheduling different periods of deprivation and integrating these with different reinforcement programs. It is anticipated that these experiments will provide information basic to the efficient initiation of studies using primates as subjects in work on conditioning factors in addiction and relapse.

X. Effect of Drug and Other Variables on "Mental Set"

This procedure, described in some detail in previous reports, may be regarded as a method for quantifying "attention." Extending this concept somewhat, the procedure as previously interpreted measures response "set" (readiness or disposition to respond). The relevance of the procedure for studying schizophrenia and for the actions of drugs on behavior depends on the findings of earlier investigators who found that certain indices of reaction time are among the most valid indicants of schizophrenia as compared with other mental illnesses. As described in previous reports, the procedure is a modification of that used by Huston and Singer (Arch. Neurol. Psychiat. 53: 365-369, 1945) for measuring auditory-manual reaction times. These are measured following visual "warning" signals at different foreperiods (the time between the warning signal and the signal to press a key) which are scheduled in "regular" and "irregular" orders. In previous years it was found that LSD-25, morphine, and pentobarbital produced changes in response set of non-psychotic postaddicts which were similar qualitatively but not quantitatively to those found in schizophrenic patients under no-drug conditions. The data on the above drugs, as well as on amphetamine, were transformed to insure homogeneity of variance, analyzed, and compared. Since that time groups of schizophrenics have been tested, and during the past year the effects of "fatigue" on set have been studied in both the addict and schizophrenic groups. The design used to isolate fatigue effects, which may influence reaction time in both groups

toward the "schizophrenic pattern," consisted of 1) comparing the first and the last 9 trials for each foreperiod series of the regular order, 2) comparing data gathered when the 2.0 second preceded the 3.5 foreperiod with data obtained when these periods were reversed, and 3) comparing reaction times found in the regular procedure when it was given first and when it was given after the irregular procedure. The data have multiplied to such an extent that analysis would be overwhelming if attempted manually. They have therefore been collated for processing by the Computing Center of the University of Kentucky (IBM-650). When the analyses are completed they will provide more clearly defined comparisons of "mental set" of schizophrenics and that of postaddicts under the above drugs, and the refined data will, at least in part, determine the extent to which the defect in set found in schizophrenia is due to alteration in the order of "warning" stimuli and to fatigue. Future work will depend in large part on the direction and significance uncovered by the computations.

SUMMARY STATEMENT
LABORATORY OF CELLULAR PHARMACOLOGY
Giulio L. Cantoni, Chief

The work of the laboratory in 1960 has continued along the four main topics which were discussed in the summary report of 1959, namely: a) mechanisms and pathways of protein biosynthesis; b) biological methylation; c) biological oxygenation; and d) alkaloid biosynthesis. The protein synthesis project may be regarded as the main project of the laboratory at the present time.

The studies on the mechanisms of protein synthesis as well as the determination of the structure of proteins as specified by the sequence of amino acids in the peptide chain are generally considered one of the outstanding problems in biology today. Until recently a relationship between ribonucleic acid and protein synthesis was predicated largely on indirect grounds, but in recent years a more direct and compelling basis for postulating a strict relationship stemmed from the discovery that a special small molecular weight RNA (S-RNA) may be directly involved in protein synthesis as an acceptor of activated amino acids and as a donor of the amino acid moiety to proteins. A concentrated, and presumably long range, effort directed at the elucidation of the chemistry, molecular configuration and biological characteristics of S-RNA appeared therefore rather attractive as an approach to the central problem of the relationship between the nucleic acids and protein synthesis. In particular, since the S-RNA exhibits marked specificity in its acceptor function towards different amino acids, it appears that elucidation of the basis for this biological specificity might represent a major advance in our understanding of a biological "coding" mechanism.

The experimental problems which need to be solved before the structure of S-RNA can be elucidated are very numerous and challenging. Nucleic acid chemistry is still in a rather primitive state and satisfactory techniques for separation of different species of nucleic acids are most rudimentary. Furthermore, specific methods of degradation which have proved of paramount importance in the determination of the amino acid sequence in proteins are almost totally lacking. Finally, techniques for separation and identification of fragments from the degradation of nucleic acids are quite inadequate. The problem, therefore, requires a long and patient search for new techniques and/or new applications of existing methods to the nucleic acid problem. No single major breakthrough may be expected, but it is anticipated that over a period of years these technical problems will

be gradually overcome and allow answers and resolutions of the central question. The laboratory's efforts have been directed toward all three of the main areas outlined above, namely, towards purification of nucleic acids, toward the study of specific and non-specific hydrolysis methods, and towards identification of nucleic acid fragments and good progress has been achieved in all fronts. (See CP 14, 16, 23, 26.)

The study on biological methylation continues to occupy the interest of the laboratory, both in the Section on Proteins and in the Section on Alkaloid Biosynthesis, and in fact, also in the Section on Cellular Regulatory Mechanisms. In the Section on Proteins, we have continued work on the enzymatic biosynthesis of methionine. The enzyme thetin-homocysteine methylpherase has been the subject of extensive study in the laboratory for a number of years. This protein has been considered to be of special interest because of its ability to readily undergo an irreversible transformation in which monomer units are united by disulfide bonds to form a continuous and defined mixture of molecular species with from one to more than 100 monomer units per molecule. Electron microscopy studies led to the suspicion that the monomer unit itself might well be made up of smaller subunits which, in fact, were revealed by treatment of the thetin-homocysteine methylpherase with relatively low concentration of organic detergents. The present evidence suggests that thetin-homocysteine methylpherase monomer indeed consists of three presumably identical subunits of molecular weight approximating 60,000. This finding is in line with recent suggestions by Kendren that the molecular weight of a single protein unit may never exceed the size of 50 to 100,000, all larger proteins being composed of subunits held together in highly specific three dimensional configuration. The biological function and significance of the enzyme thetin-homocysteine methylpherase remains the object of speculation, particularly in view of the discovery in this laboratory of another liver enzyme, betaine-homocysteine methylpherase, whose more natural substrate specificity suggests it plays a leading role in the physiological synthesis of methionine from betaine-homocysteine.

The Section on Alkaloid Biosynthesis, now in its second year of existence, has continued studies on the biosynthesis of the alkaloid N-methyltyramine, hordeine and gramine by cell free extracts of barley or millet. The methyl group of these compounds is donated by S-adenosylmethionine. Several other compounds which have been suggested in the literature as possible methyl donors are inactive in this system. These findings were extended in a series of experiments in which it was shown that

barley can synthesize S-adenosylmethionine identical to that found in vertebrate even to the extent of having the same stereochemical configuration about the asymmetric sulfur and oc-carbon atoms. Together, these facts indicate that the predominate pathway of plant transmethylation does lie through S-adenosylmethionine just as it does in vertebrates and microorganisms.

These findings illustrate once again the value of studying fundamental enzymatic mechanisms in whatever biological material is most convenient with the assurance that the facts in a given form may well apply to widely divergent species. Although transmethylation is apparently extremely important for all forms of life, the enzymatic mechanisms at work here are imperfectly understood and it is hoped that further work with botanical systems may clarify details of the process.

A matter which requires further exploration is suggested by the structural resemblance of two of the particular plant alkaloids studied to the adrenal hormones of mammals and of a third to mammalian serotonin. If the role, as yet unknown, of these compounds in plant metabolism can be elucidated, we may gain thereby an important lead to discovering the role of these neurohormones and of chemically related hallucinogenic materials.

The formation of the alkaloids now being studied is known to be under not only genetic control, but under other controls as well, so that the formation occurs in a dramatic outburst at a specified stage of ontogenesis and in restricted types of tissues. It seems not unlikely that a study of the interplay of the control mechanisms which are at work here will give insight into the important question of how enzyme formation and activity is governed in higher organisms. The genetic, environmental, tissue specific and hormonal factors cooperating in this system are undoubtedly complex but it is hoped that the relative ease of experimental control of the plant will aid considerably in work on this question.

The Section on Cellular Regulatory Mechanisms continued its fundamental studies of biological oxygenation. The reactions which have been under investigation, namely, the hydroxylation of phenylalanine and of DOPamine present interesting similarities. Both reactions require, in addition to various and specific enzyme fractions, vitamin coenzymes which play the role of electron donors in the reaction in which they participate. Although the biochemical mechanisms of both hydroxylation reactions may be similar, the vitamin cofactors which are involved in these reactions are different, namely, a pteridine compound

analogous to, but not identical with, tetrahydrofolic acid functions in the phenylalanine hydroxylation while ascorbic acid plays a role in the DOPamine hydroxylation reaction system.

Earlier work from Dr. Kaufman's laboratory has established that reduced pyridine nucleotides were necessary for the enzymatic conversion of phenylalanine to tyrosine. The participation of reduced pyridine nucleotides in an oxidative reaction was an intriguing aspect of the problem which has now been answered since it has been shown that the function of the reduced pyridine nucleotide is to maintain the pteridine cofactor in its reduced tetrahydro form.

The significance of Dr. Kaufman's studies on the enzymatic conversion from phenylalanine to tyrosine to the pathogenesis of the disease of the oligophrenia phenylpyruvica is self evident since this disease is characterized by a genetically determined inability to effect this conversion. One of the difficulties which has been hampering progress in studies of the relationship between the metabolic defect and the physiopathology of the disease has been the unavailability of an experimental animal showing this disease. With the goal of finding such an animal, several long term experiments have been initiated. In one direction, it has been found by Dr. Kaufman that a genetic strain of rat (developed by Kretch) which shows poor maze performance also has lower levels of phenylalanine hydroxylase than in a control strain of animals. There are indications that some of the physical properties of this enzyme may actually differ in these two strains being less stable in vitro from the behaviorally inadequate animals. In another approach, Dr. Kaufman and Dr. Goodfriend have kept weanling rats on high phenylalanine diets, an environmental situation which mimics that faced by the phenylketonuric infant. After several months on this diet the animals are tested for maze performance. Preliminary results indicate that rats kept on this diet give a definitely poorer maze performance. It may prove to be possible, through either of these lines of investigation, to produce a "mentally retarded" experimental animal.

Studies on the biosynthesis of norepinephrine are of particular relevance and complement beautifully the studies of Drs. Mudd and Mann in the Alkaloid Section.

1960 has seen the initiation of the sabbatical program for the Laboratory of Cellular Pharmacology. Our two senior members, Dr. Kaufman and myself, have taken advantage of the unique opportunity which has become available at the NIH to

explore new areas of research endeavors. I have chosen to divide my sabbatical leave into two to three periods of "research intermissions." The first installment was completed in 1960 by a visit to the Institute of Genetics, University of Pavia, where I participated in the Institute's work in the area of bacterial genetics. The results of my sabbatical were most profitable for they enabled me to acquire a better grasp of the theoretical and technical problems in the field of modern bacterial genetics.

Dr. Kaufman is spending a year in the Laboratory of Professor Ernst Hadorn at the University of Zurich, exploring the general problem of cellular differentiation, particularly in relation to the regulatory role of the gene or gene product in ontogenetic development. The project on genetic and developmental studies on tryptophane pyrollase in drosophila melanogaster is a clear indication that he is making rapid progress in this endeavor and deriving from it great benefit and stimulation. On the whole, there is no doubt that the introduction of the sabbatical program at the NIH will greatly strengthen the research program of the Laboratory of Cellular Pharmacology as it undoubtedly will for other laboratories.

In 1960, the Laboratory enjoyed the collaboration of Dr. Claude Blanc, formerly of Marseille University; Dr. Maxine Singer, NIAMD, Dr. Theodore Goodfriend, formerly with the Endocrinology Branch, NCI; Dr. Peter Weiss, NIMH; and Dr. C. W. Clancy, University of Oregon.

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LABORATORY OF NEUROPHYSIOLOGY

Wade H. Marshall, Chief

Investigators in the Laboratory of Neurophysiology, NIMH-NINDB are working on a great variety of fundamental problems of the nervous system. Problems range from the initiation of the nerve impulse to social behavior of the South American Squirrel Monkey (Saimiri sciureus). Material used extends from the "simple" plant cell of Nitella, which reacts with an action potential resembling a nerve cell, to the whole brain of the monkey.

The Section on Special Senses, led by Dr. Ichiji Tasaki, has continued work of fundamental importance on the analysis of the excitable membrane. The squid nerve has been exploited with most ingenious experiments. Tracer work with experiments designed and interpreted on the basis of irreversible thermodynamics was done on both animate and inanimate systems. It was found that the squid nerve membrane was far more permeable to cations than to anions. This fact was related to the fixed negative charge hypothesis originally advanced by Michaelis and Teorell (the latter was a collaborator in this research in 1959). This theory predicates a membrane containing internal negative charges which should tend to attract cations. Following up the consequences of this concept, Dr. Tasaki hypothesized that divalent cations such as Ca^{++} or Mg^{++} should abolish a prolonged action potential (upper stable state of Tasaki) and that the reaction should be endothermic.

In a most effective series of experiments, Dr. Spyropoulos, using the single node preparation of the toad nerve, produced conclusive evidence for such a theory. Delivery of a small amount of Ca^{++} ion to a node in the upper stable state immediately returned it to the lower stable state, i.e. abolished the action potential and returned the membrane to the resting state. Since the displacement of K^{+} ion by Ca^{++} is an endothermic reaction, it was hypothesized that sudden heating of a node would accomplish the same effect. This was found to be true. Conversely, release of Ca^{++} ion from the negative sites in the membrane should be exothermic and a sudden pulse of cooling was found to initiate an action potential in a resting membrane. This is in impressive agreement with the theory, or at the very least, constitutes reasonable ground for further work along this line of approach. According to Dr. Tasaki's theory the membrane in the resting state is locked in because the divalent Ca^{++} ions successfully compete with K^{+} ions at the negative sites in the membrane.

The movement of Na^{+} and K^{+} ions which accompanies and follows the action potential has been further studied with tracer techniques using the fractionator. The fractionator was first

introduced by these investigators in 1959. This important tool has been further developed and now occupies a secure place in the analysis of the nerve impulse. With this device it is possible to get time distributed samples, with a time resolution as short as 25 msec., of tracer bearing wash fluid from a segment of nerve. By prolonging the nerve action potential it is theoretically possible to ask the question: Is there really a time succession of Na^+ flowing in and K^+ flowing out of a nerve during the rising and falling phases of the action potential? Results so far obtained indicate that both K^{42} and Na^{24} flow out of the axon both at beginning and end of the action potential. Further development of the fractionator toward shorter time resolution and greater sensitivity is proceeding. These experiments have been extended to a primitive plant cell (Nitella) which also exhibits an action potential.

These researches have gone far to elucidate general properties of excitable membrane and to permanently change our conceptions of the nerve impulse.

Three visiting scientists, Dr. A. Arvanitaki-Chalazonitis, N. Chalazonitis from France, and Dr. T. Oikawa from Japan collaborated in these researches at the Marine Biological Laboratory, Woods Hole, Massachusetts.

The Section on the Spinal Cord, led by Dr. Karl Frank, has continued in important work on fundamental analysis of the nervous system. The investigation of the roles of the principal parts of the neuron, axon and axon hillock, soma and dendrites has been extended. The technique employed (described in last years report NINDB-NP-SC-3) permits activation of a single neuron in a large population. This allows examination of the electric field around the neuron. It was found that the fields for the two main features, the A and B spikes, were not coextensive and further that the B spike was followed by a positive afterpotential. Dr. W. Rall, Office of Mathematical Research, NIAMD, has been a valuable collaborator on this project. His computations of external fields of this type not only are substantial creative contributions, but are also in excellent agreement with the experimental data.

Dr. T. Oikawa, Visiting Scientist, has investigated a large nerve cell in the goldfish. The data strongly suggest that the antidromic impulse does not invade the soma and dendrites. No evidence was seen of separate A and B spikes common to many other types of cells.

Drs. P.G. Nelson and S.D. Erulkar have been investigating basic mechanisms of hearing in the auditory system at the collicular and geniculate level in the brain. They have observed both

inhibitory and excitatory processes in the same cell depending on which ear was stimulated. One of the fascinating problems of hearing is the fact that the human can discriminate time differences of 10μsec "between the ears". Studies of this type will eventually explain how times of arrival to the two ears can be analysed to this level of precision.

Drs. Frank and Nelson have undertaken an ambitious but not unrealistic study of the fundamental mechanisms of learning. One of the hypotheses of learning involves the anatomical and functional organization of synaptic connections. In this project methods are employed which permit long time activation of certain pathways to the spinal cord neurons. After periods of time, the physiological characteristics of neurons so activated will be compared with control neurons on the opposite side of the spinal cord. The time has come for such developments and Dr. Frank has other projects under consideration in this field of study. It is particularly pertinent that this Section go into this area of research because of the broad and detailed experience acquired in the past decade.

The Section on Membrane Physiology's program is directed into the general area of the ubiquitous excitable membrane and is currently investigating muscle fibers. The surface membrane of both nerve and muscle fibers is electrically excitable, i.e., a wave of self-propagating electrical activity travels along it. Ionic currents carried by sodium and potassium movements are reponsible for this activity and the mechanism of electrical excitability has many features common to nerve and muscle. In muscle, however, there is an additional mechanism for the passage of potassium into or out of the cell. This mechanism is not necessary for the production of electrical excitation. An explanation of the additional passage of potassium that evokes the submicroscopic internal tubular structure of muscle is in accord with many of the experimental observations. The tubules could be the pathway for the additional passage for potassium Such a system could relay the electrical activity from the surface membrane of a muscle fiber to the internal trigger areas for contraction. Some mechanism of this sort is necessary to activate the internal contractile process with only a short delay after the electrical activity at the surface. The one considered here is admirably suited for this purpose. The work of the Section on Membrane Physiology is to investigate these intriguing fundamental speculations.

The Section on General Neurophysiology has been involved in intracellular analysis of the pyramidal cells of hippocampus, patterning of somatic sensory impulses in cortex and thalamus, work on direct electrical initiation of the cortex and correlation of slow electrical changes and pH of the cerebral cortex.

The hippocampal project has been pursued in a brilliant and energetic way by Drs. Eric Kandel and Alden Spencer for a period of over two years. They have worked out important constants of the pyramidal cell and secured much information on synaptic activation and reaction properties of the pyramidal cell. This work was extended to a study of convulsive seizure patterns. Drs. Kandel and Spencer have received unusual recognition for men of their age. They have been invited to famous laboratories and have also accepted invitations to present their work in a symposium to be published in "Epilepsia", and a presentation to a symposium entitled "Current Problems in Electrobiology" conducted by the American Association for the Advancement of Science and the New York Academy of Sciences.

Dr. Barbara Renkin has proceeded with analysis of sensory patterns, relating cortex and thalamus. This academic year she is a Fellow of the National Science Foundation and is on leave from this laboratory and is working with the distinguished neurophysiologist, Professor Granit at the Karolinska Institute in Stockholm.

Mr. Anthony Bak is developing a brilliantly designed averager for retrieving data from noise. The final model is not yet completed, so final judgment cannot be made at this time. It will be used by Drs. Frank, MacLean and others. Mr. Bak has also given valuable collaboration to several projects in the laboratory. Among these is his introduction of the cathodyne, which was crucial in Dr. Spyropoulos' project on the control of nerve impulse in single fibers by chemical and thermal manipulation.

Other work in this section is proceeding on specific relation of pH changes in cortex and spreading cortical depression of Leao. There is also a general project underway on cortical reactions involving analysis of dendritic and soma activity using implanted electrodes.

The Section on Limbic Integration and Behavior, led by Dr. Paul D. MacLean, is very busy with important contributions to the general area of brain and behavior. The squirrel monkey from South America is the principal experimental animal used by this laboratory. Further developments of techniques for employment of this monkey have been made and the stereotaxic brain atlas, (project M-NP-LI-9, 1959) is approaching completion. The work of this section uniquely combines studies of neuroanatomy, neurophysiology and behavior.

Drs. Gergen and MacLean are proceeding with general physiological anatomical analysis of the hippocampus. Under

chlorolose anesthesia they have found visually evoked reactions. Search for representation of other exteroceptors in this primitive part of the brain will be made.

The study of convulsive reactions in the hippocampus and effect of these reactions on other parts of the brain and, in turn, on total behavior has been continued. It is known that the hippocampal part of the limbic system is peculiarly sensitive to convulsions and convulsive like reactions. These studies of mechanisms of the total system reactions are of great importance for understanding brain and behavior.

Work on localization of gential function has been continued with the monkey. Dr. MacLean is the first investigator to systematically demonstrate and study the direct physiological and anatomical loci in the brains of animals, electrical and chemical activation of which produced specific sexual responses. This important work is proceeding and an entirely new chapter is being developed in knowledge of brain. As an important example, it has been found that electrical stimulation of the anterior thalamic group produces penile erection. This is specific for the medial part of the medial dorsal nucleus. This nuclear group is directly connected to the phylogenetically new frontal lobes. This constitutes the first proof of a specific anatomical and functional relation of the frontal lobes and a primitive function of the "old" limbic system. This mechanism probably explains some of the behavioral changes observed in patients after frontal lobotomy.

As an important corollary to all work in this section are studies of individual and social behavior of the squirrel monkey.

The senior scientists in the laboratory have received many invitations to present their work at scientific and educational meetings. This shows that the work of the laboratory is respected and is at the very least accepted as well as can be expected of current research.

Annual Report of the Section on Technical Development, NIMH Calendar Year 1960

In the calendar year 1960, the Section on Technical Development has completed approximately three hundred and fifty projects in support of the Basic and Clinical Research Program, NIMH-NINDB. Some of these will be itemized later in this report. The majority of work has been in response to direct requests by the investigator, while some originated internally. Other functions and services performed by the Section will be outlined, along with a few words in regard to the future operations. Needs will be mentioned along with how they have been met or should be met.

In line with the recently emphasized policy of making "Excess the First Source of Supply", this Section has worked closely with Mr. Paul Schenk of the Property Utilization Unit in an endeavor to fill as many of our needs as possible from excess materials made available from other Federal Agencies. Due to the efforts of Mr. Schenk and his staff, this Section has obtained many thousands of dollars worth of serviceable equipment and components. On a prorated basis, this will result in a very significant dollar saving over a period of many years. As the mechanisms for obtaining excess materials are further developed, it will become increasingly easier and quicker to garner a portion of our working needs in this manner. Money saved in this manner can be applied towards the purchase price of new equipment for our "Repairs and Calibrations" unit. In many cases, components and equipment have been reissued by this Section to other laboratories and, in the case of real abundance, have been issued to laboratories in the NHI and NIAMD. An item of interest is the acquisition of five 35mm moving frame cameras, which we feel can be adapted to the program needs. The original cost was about $4000 each. We obtained them for freight charges.

Components other than Federal Surplus continue to be available on a limited basis for issue to the various laboratories. As in the past, laboratories needing components in quantity are encouraged to furnish their own stocks. However, I believe that purchase orders for mechanical and electronic components originating in other laboratories should now be screened by this Section to avoid the purchase of materials which may be on hand in this Section and excess to our needs. Also, equipment of some kinds is available for loan to help forestall delays in procurement. An exception to this policy will be found in the "Repairs

and Calibrations" area where our standards will not be available for loan.

Reference is made to the memorandum issued by the Director of Basic Research NIMH-NINDB on April 13, 1960, to the Laboratory Chiefs, Basic Research Program in regard to the more efficient use of storerooms. Per request, this Section has assumed the responsibility of clearing these areas (3N-264 and 2D-35) and creating a combination service area and live storage area facility in each room. In one room (2D-35) the facility is operative, in the other (3N-264) we are still trying to recruit a competent person for the assignment. Numerous items have been removed for remote storage in Building 9 and more will be when the Building 9 areas can be improved security-wise. Work requests have been submitted. In passing, I want to thank all the scientists for their ready co-operation.

Three persons were added to the Section during the year. In October, Mr. Ross R. Snider, Supervisory Electronic Engineer came on duty in the position of Section Chief. During July, Mr. Leo G. Leitner, Electronic Technician, entered on duty. Mr. Snider will provide the high-level professional direction the Section has lacked in recent years. Mr. Leitner is scheduled to be a part of the Repairs and Calibrations service which we will provide in the future. Also, for the first time the satellite concept is in practice. Mr. John A. Cooley, Electronic Technician, was brought on duty in October as a member of this Section but attached to the Laboratory of Psychology, NIMH, on a full-time basis. He will have as his responsibility, all the instrumentation problems of that Laboratory, less the Section on Animal Behavior, as far as he is capable and equipped. We had one summer employee this year, Mr. Gary Gloyd. He was a great help in our storeroom reorganization and in the "Excess Property Utilization Program".

Having additional personnel this year was responsible for our being able to detach two men to the Marine Biological Laboratory, Woods Hole, Massachusetts, during the summer. Mr. Byrne was TAD to the Section on Special Scenses, Laboratory of Neurophysiology for eight weeks and Mr. Leitner also was TAD to Section on Special Scenses, Laboratory of Neurophysiology for eight weeks. The two periods were partially overlapping due to the needs of the scientists at Woods Hole. This is cited as an example of the direct assistance concept described in last year's report. We were able to devote some 640 regular man-hours of this direct assistance, in a lump sum, so to speak, for the first time.

The Section's man-hours are divided into various categories, as they have been in years past. Time is divided between the new and the old. Design, development, construction and consultation

occupy their portion while maintenance, repair and modification occupy theirs. Much more needs to be done in the latter group. Our "Repairs and Calibrations" unit is intended to help rectify a situation which finds many meters and recording devices throughout the Program badly in need of calibration.

Our filing system and library continue to be available to interested persons. Both have been methodically expanded during the year and will continue to be. The library contains books specifically on Medical and Biological Physics and Electronics as well as general texts and reference works in the physical sciences. The literature files are maintained up-to-date by virtue of being on manufacturers' and distributors' mailing lists, as well as scanning technical publications for new items and new manufacturers and/or subsidiaries.

Various instrumentation problems have either not been started or not completed due to the Section's workload. Paramount among these are modification kits to reduce 60 cycle interference and reduce artifacts in EEG recordings, and battery replacement power supplies for use with preamplifiers requiring DC filaments and plate voltages. In regard to EEG records, the goal is a machine which is not so sensitive to AC pick-up when other equipment is operated in the same immediate area. In regard to the battery replacement supplies, we would like to eliminate the considerable expense of batteries as well as reduce the inopportune breakdowns due to battery failure. Other projects that have lagged, due to the continued non-availability of uninterupted time, are a remote positioner for micropipette electrodes and a vibrating drive to permit penetrating single cells without moving them.

There have been two changes in the Section. One is a matter of policy while one is a functional change. We have had to reduce sharply the amount of work done in our shops personally by the various investigators. With the additional people in the Section and without additional space for them to work, safety and efficiency dictated this change in policy. However, we can now furnish faster service on this type of work by members of the Section. The new function will be a "Repairs and Calibrations" unit, now in the embryo stage, which will, as its sole duty, engage in the preventitive maintenance, repair and calibration of equipment in the Basic Research Program. We will attempt to work out some mutually convenient scheduling in this regard.

Included below is a brief run-down on a few of the projects completed or partially completed this year.

Three additional slave scope assemblies are nearing completion similar to the one mentioned in last year's report. Minor design variations were called for and were incorporated.

Two slave scopes are for use with a single beam oscilloscope and one for a dual-beam scope. These units permit the simultaneous viewing and photographing of an oscillographic waveform, along with various other data superimposed on cathode ray tube by mirrors.

A thermoelectric heating and cooling system was developed, making use of the properties of the relatively new thermoelectric junction. By causing various calibrated currents to flow, it is possible to produce desired temperatures. The direction of this current flow determines whether heating or cooling takes place and the amount of current determines actual degree change.

A quadruple photocell marker system was developed for psychological experimentation. Each of the four channels are actuated by light pulses on the order of 10 milliseconds. Fast output relays are used to perform controlling functions. Regulated power is provided for amplifier stages and for the photo conductive cells.

A response timer and counter was designed and built for child development studies. Infants are presented with attractive switches which control various colors and combinations of lights. Number of responses and time per response are counted and recorded.

Numerous plexiglass chambers have been machined and assembled for various laboratories. Some provide for the flow of liquids to maintain a biological preparation at constant temperature. Others provide the facility for dissecting nerves, etc. One was built of a size and shape to restrain a live fish during experimentation.

A motor driven switch was designed and built in co-operation with Laboratory of Neurophysiology. This consists of ten magnetic reed switches, arranged in a radial pattern around a revolving permanent magnet. The switches are energized sequentially by controlled magnetic fields. Since each reed switch is sealed in a vacuum, the switches provide the high open-shut resistance ratio necessary to any sampling system which involves the charging of capacitors for extracting signal from noise, when the signals are repetitive but considerably smaller than the noise.

Several electrometer input preamplifiers have been constructed from specifications previously established. Also, a chopper-stabilized preamplifier was built and tested. This enables small DC signals to be recorded without the super-regulated power necessary if the amplifier is direct coupled throughout.

Several important areas of endeavor face us in the coming year. Among these is the dual closed circuit television monitoring system for the sterile surgery wing. All the physiological information which is gathered from the patient is then fed to the recording room. The graphic records are televised and displayed on monitor cathode ray tubes for the surgeon to refer to as the operation progresses. We also have the EEG, EKG, EMG, GSR, CO_2 and temperature recorders to install and maintain. When this system is in operation it will require the full time of at least one capable man merely for maintenance.

Other problems center around the tape recording of physiological data and the preparation of this data for computer analysis. We have made further progress in the positioning of micropipettes and the coming year should see an adequate instrument for this purpose. Our contribution to the Research Program will continue to increase in all the applicable fields as the Section continues to grow in competence and responsibility.

Laboratory of Neurochemistry

1960

Robert B. Livingston, M. D.
Acting Chief

As of the end of June 1960, the Basic Research Program, NIMH-NINDB *per se* was dissolved and such Programs independently established within the respective Institutes. The Laboratory of Neurochemistry having been a combined-Institute operation, i.e., the Section on Lipid Chemistry under the direction of Dr. Roscoe O. Brady being the NINDB-supported facility and the Section on Physical Chemistry under the leadership of Dr. Sidney Bernhard conducting research through NIMH support, was one of several affected by this transition.

Having been Acting Chief of this Laboratory for over three and a half years I am impelled by my esteem to express sincere admiration and respect for each member, both past and present, of the Laboratory for individual intellectual endeavors and the high quality of research performed. Because of the scarcity of space, this Laboratory was precluded from developing beyond its initial phase and operated under extremely difficult conditions. Despite this, both Sections through research accomplishments are recognized nationally and internationally in the field of medical research and have added to the prestige of their respective Institutes and that of the National Institutes of Health.

Summary of Reports for Calendar Year 1960

Section on Physical Chemistry

Sidney A. Bernhard

The polynucleotide complex of polyinosinic and polycytidylic acid is known from previous work in this Section to give a diffraction pattern resembling that of natural ribonucleic acid. Further investigations have shown that it is possible to produce a crystalline form of this material. X-ray investigations have demonstrated that the structure of the crystalline form is very similar to that of deoxyribonucleic acid. In addition, it has been possible to transform the non-crystalline form into the crystalline form in the fiber. This evidence indicates that the structure of the natural ribonucleic acid is, in its ordered regions, two stranded in form with hydrogen bonded base pairs similar to those in deoxyribonucleic acid. Large single crystals have been grown of the proteolytic enzymes, chymotrypsin and nagarse. An investigation of the properties of the nagarse shows that it is possible to proceed further into a detailed investigation of the molecular structure of this material.

Perhaps the single most important discovery in the work on aggregation of dyes bound to polyanions is that the structure of a polyanion determines in part the strength of dye-dye interaction so that the color of bound dye can tell us about the polyanion to which it is bound. We have collected a considerable body of data which supports the generalization that the more rigid and well ordered the polyanion, the weaker the dye-dye interaction. For example, all samples of native, well ordered deoxyribonucleic acid (DNA) examined show the same low value of this interaction, but when they are disordered by heat denaturation, the strength of the interaction increases. This observation has been developed to the point where the color of bound dye can be used to determine the degree of nativeness of DNA specimens. Applying this general principle to structural changes in synthetic nucleic acids it has been possible to confirm certain hypothesized transitions. A quantitative method of analysis in the microgram range for nucleic acids, mucopolysaccharides, and synthetic polyanions has been developed. A detailed study of the interaction between dyes bound to plant, animal and synthetic acid polysaccharides has been completed. As a result of this work it is now possible to differentiate among them as well as to relate the observed differences in the staining properties of these polymers to the type of binding site, and their number and relative locations on the sugar moieties.

In the study of the synthesis and properties of enzyme models the testing of detailed theories of enzymic catalysis by chemical synthesis of model compounds and studies of their catalytic and chemical properties is being carried out. Ultimately,

via such investigations, to synthesize a model enzyme.

A theoretical approach to the problem of sequence determination in proteins is being studied. The major block to rapid development of this field is that the experimental determination of the amino acid sequence in even a single protein is an extremely difficult and laborious affair. The choice of methods of protein fragmentation, average size of peptides, selection of peptides to be analyzed, and amount of sequence data to be obtained from each peptide as well as the method for using the data collected in reconstructing the overall sequence are all a matter of choice. We have been examining this problem from a logical-mathematical point of view in an effort to find an experimental design which will minimize experimental effort and an information processing system which will utilize experimental data optimally.

Investigations are being carried on to produce and investigate natural variants of a proteolytic enzyme. In order to examine the enzymatic mechanism and substrate specificity of enzymes, it would be extremely valuable to have available different forms of the enzyme having altered catalytic properties and specificity. By selecting for mutant forms of a bacterial enzyme, it is hoped that a large number of such variants can be produced.

Laboratory of Neurobiology

1960

Robert B. Livingston, M.D.
Chief

The Surgeon General, on October 18, 1960, approved the establishment of the Laboratory of Neurobiology within the Basic Research Program of the National Institute of Mental Health.

This Laboratory will conduct research on the brain using mainly neuroanatomical, neurophysiological, biophysical and behavioral techniques, in the search for an improved understanding of perception, learning, memory, judgment and other complex functions. Specifically, studies will be carried out on:

i) Mechanisms involved in the central control of sensory transmission;

ii) Mechanisms underlying the prolonged effects of certain sensory stimuli;

iii) Mechanisms of integration between sensory and motor pathways; and

iv) Chemical and metabolic linkages related to electrophysiological mechanisms of nerve conduction.

We were fortunate in having the following join the staff of this Laboratory:

i) Dr. Bo E. Gernandt, Visiting Scientist, continuing his fruitful investigations of spinal, cerebellar and brainstem mechanisms underlying posture and locomotion. Since 1958 and until joining this Laboratory, Dr. Gernandt had been affiliated with the Laboratory of Neurophysiology under the leadership of Dr. Wade H. Marshall.

ii) Dr. Muneo Shimamura of the Department of Physiology, Hokkaido University School of Medicine, with wide experience in brainstem mechanisms controlling motor functions, currently a Visiting Scientist, is collaborating with Dr. Gernandt.

iii) Dr. Arnold Starr, Research Associate within the NIH Research Associates Program, having completed a two-year residency in Neurology under the aegis of Dr. Derek E. Denny-Brown, is studying mechanisms underlying

prolonged effects of sensory stimulation.

iv) Mr. Gabriel Frommer, Commissioned Officer in PHS, a candidate for the Ph.D. from Brown University, with experience in thalamic responses to taste stimulation under the tutelage of Dr. Carl Pfaffmann, is investigating mechanisms involved in the central control of sensory transmission.

v) Mrs. Rosalind Marimont, Theoretical Mathematician, with twelve years' experience in the theory of higher forms of mathematics and computer logic, is studying the focal requirements for pattern recognition.

The Laboratory has been in existence for so short a time that no progress can be reported. Until additional space becomes available we will not be able to begin work on the chemical and metabolic mechanisms relating to electrophysiology.

Annual Report--1960
Clinical Investigations
National Institute of Mental Health

The reports of the laboratory and branch chiefs which summarize the studies now underway in the Clinical Investigations program demonstrate clearly the nature of the progress made during the past year. Although some projects have been brought to highly successful conclusion and others are far enough along to promise significant results, in my opinion the most important and promising development has been the increasing pervasiveness of a truly interdisciplinary atmosphere. By this I do not refer simply to such studies as the coping project in the Adult Psychiatry Branch or the schizophrenia research in the Laboratory of Clinical Science. These and many other investigations by their very nature demand the participation of a varying number of the behavioral disciplines which are strongly represented in our program. Nor do I imply, of course, that NIH has in any sense a monopoly on interest in the prosecution of interdisciplinary research. But those of us who have spent our professional lives in hospitals or in university departments are repeatedly impressed by the unique character of the Clinical Center setting. The interaction at the regular staff conferences over the eight years of our existence has had a noticeable impact. The individual social or biological scientist no longer approaches a representative problem even in his own discipline without some consideration of its broader implications. Such thinking, by taking into account a wider range of possibilities, leads to a more critical evaluation of the phenomena we are attempting to understand. As the range and depth of our studies show, this atmosphere has not had a stifling effect upon individual initiative; rather, it has promoted careful attention to methodology, precise evaluation of results, and, what is most important, a search for more powerful conceptualizations.

In previous reports it has been noted that external circumstances dictated the establishment of our several laboratories and branches almost as islands quite distinct from one another. To some degree and in some areas it is desirable that this should remain the case. But it has been interesting and stimulating to note the spontaneous appearance of several areas convergence - to name only one, the impact of the family on behavior and personality development is being studied from various points of view by each of the major research groups. The organization of Clinical Investigations was designed to foster the development of such convergences of interest in the hope that they might lead to significant advances in behavior theory.

In the last annual report I discussed some of the external and internal conditions which affect our creativity, our sense of fulfillment and satisfaction in our work, and our productivity. These are so commonly matters of concern for any program director that mention of them might have seemed almost banal. In retrospect the matters which were uppermost in my attention at the time were related to the desires of the investigators for a greater degree of participation in decision-making which led to the development of the Assembly of Scientists of NIMH-NINDB, and to the fact that each month brought attractive, and in several instances successful, offers to our staff from universities and other research centers. Some turnover of staff is desirable, of course, to keep a group from becoming too in-bred, and some is to be expected in any event. But the achievement of the long-term goals we have set for Clinical Investigations do depend in part upon the continued interaction of a number of the more senior staff. Further, when valued members of its staff take appointments elsewhere, it behooves any institution to scrutinize its own practices once more to assure that everything that can be done to promote the success of its mission is being done.

My concerns of last year seemed to have had almost a prophetic quality when three of our laboratory chiefs were simultaneously seriously considering offers of important university posts. Dr. John Clausen accepted the directorship of the Human Development Center at the University of California and Dr. Seymour Kety has accepted the Chair of Psychiatry at Johns Hopkins University Medical School. Although we were mindful of the fact that 51% of the chairmen of departments queried by the authors of the Academic Marketplace placed their own departments among the top five in the country, all this occurred at a time when we honestly felt that our own research was stronger and more solidly based than it had ever been previously, that the problems of development were largely successfully worked through, and that the next ten years might be expected to show what this type of research organization could accomplish - a research organization which, unlike some others, had been largely shaped by its members.

In thinking back to the concerns we have had about NIH as an institution in which one might spend his professional life, I do not believe that we have identified any issues not mentioned in the 1959 report. It is generally felt that we are making progress toward a more effective delegation of decision-making in this large organization, and that we are developing reasonable methods for program evaluation. Some problems related to these areas are not solved, but in a living dynamic organization these and similar matters are the focus of continuing interest and can never be permitted to become ossified into a body of inflexible regulations.

Perhaps of all the issues mentioned in the last report, the one most pertinent to our immediate situation is the concept of the full-time research organization. What kinds of institutional supports need to be built into it to promote the total professional development of its members at various phases of their professional careers, and at various phases in their periods of creativity? The university affords supports for research, supports for teaching, and - for the clinician - supports for practice. One may engage in any or all of these activities and feel that he is making a worthwhile contribution. The development of suitable supports for our institution is a task for the investigator and the administrator, and in my opinion the ultimate success of NIH as a research institute will be largely dependent on the results of our joint efforts.

Finally, the year has increased our debt to Miss Agnes Middleton, Mr. Stanley Hirsch, Mrs. Hazel Rea, and Dr. William C. Jenkins. Miss Middleton, Director of Psychiatric Nursing, and Mr. Hirsch, Director of Psychiatric Social Service, and their staffs have been called upon not only to carry out most efficiently all those essential services which nurses and social workers contribute in every therapeutic setting, but also to work with a wide variety of normal volunteer subjects and to assist in the development and operation of a system of recording upon which essential research findings depended. In addition to the specific contributions which they have made to the research data, all of us - patients, normal control subjects, and investigators alike - have come to rely upon them and their staffs day in and day out and perhaps to take for granted the maintenance of the optimum human environment without which our work could not have gone forward. Because of the nature of our program, which includes so many psychosocial studies, Mrs. Rea, our administrative officer, is regularly faced with problems for which no routine solution is to be found in an institution largely devoted to studying the organic aspects of disease; in addition, she has had to develop a completely new set of procedures in connection with the Clinical Neuropharmacology Research Center at Saint Elizabeths Hospital. She has brought to her duties a combination of resourcefulness, energy, and tact which has dissolved difficulties that often seemed insoluble. Dr. Jenkins, Chief of Clinical Care and for six years our representative on the Medical Board, has carried the overall responsibility for the clinical aspects of the entire service. He has interpreted research needs to Clinical Center and NIH administration, Clinical Center needs to the research group, and he has practiced preventive maintenance so effectively and yet so quietly that few of us realize how much we have all benefited directly from his efforts and indirectly from the general esteem in which he is held by professional colleagues and patients alike.

Robert A. Cohen, M. D.

Annual Report of the Chief of Clinical Care
Wm. C. Jenkins, M. D.

Perhaps the most significant development in this area during the past year was the establishment of a nursing unit for interdisciplinary research of all the laboratories and branches of the Clinical Investigations program. A committee made up of representatives of each of the branches and laboratories, the Chief of the Psychiatric Nursing Service, the Supervisor of Social Work for NIMH, and the Administrator of the Nursing Unit--Dr. Harold Greenberg--from the Office of the Director of Clinical Investigations, consider and approve the various research projects proposed. It is hoped that this will develop into a flexible arrangement which will make possible a variety of studies, at times with mixed diagnostic categories of patients, and will enhance the possibilities of productive interdisciplinary research. Projects presently being carried out on this unit include studies of the depressive states, the aging process, and periodic catatonia. Other studies of patients with acute schizophrenia and of schizophrenia in twins, are in prospect for the immediate future. The enthusiasm and productive efforts of all the staff members involved promise well for this venture.

The designation of a separate nursing unit for interdisciplinary research for all the laboratories and branches became possible with the consolidation on to one unit of the Adult Psychiatry Branch studies of families of patients with schizophrenia, and the studies of first year college students with psychiatric illness requiring hospitalization.

For the past year two of the five nursing units allocated to the NIMH have been used for normal volunteer subjects. Ninety individuals have been admitted to our nursing units during that time. We have enjoyed the excellent services of the Office of the Director of the Clinical Center in recruiting and arranging for these people to come here from colleges, church organizations, etc. They provide us with the opportunity for carrying out a number of studies of normal individuals, as well as serving as normal controls for a number of other studies of patients. In addition, 97 normal volunteers were seen in studies requiring outpatient visits only for some 1,500 visits. These subjects were seen in studies carried out for the most part by the Laboratory of Psychology and the Child Research Branch.

Requests for psychiatric consultations by staff of the other Institutes and the Employee Health Service totaled 156 for the year ending June 30, 1960. During the past year, at

the request of the National Cancer Institute, we have arranged for one of our psychiatrists, Dr. Noel Schweig, to attend a regular conference of nursing and medical staff on one of the Nursing Units of the NCI. We have also arranged for one of our psychiatric consultants, Dr. Joseph Noshpitz, to attend a regular weekly conference on problems of children with Leukemia who are hospitalized on another Nursing Unit of the NCI.

Consultation requests for psychological testing have been met primarily by Dr. Isabelle Kendig, of the Laboratory of Psychology, as part of her research interest in self-concept and body image. Dr. Kendig has recently retired and we are now in the process of recruiting a suitable individual to take responsibility for service needs for psychological testing on our own nursing units, as well as for meeting requests from other Institutes.

The special nature of the Clinical Center, in which central services are provided and administered separately from the investigative and clinical care provided by the NIMH, calls for many interchanges between staff of the various central services and NIMH staff. That there is so little friction, and that so many potential problems get worked out in an effective and cooperative manner, is a tribute to the many members of the staff of the Clinical Center with whom we closely work. An example of this working relationship, but by no means the only one, was that of the nursing staff of Nursing Unit 2-W, who during a prolonged and complex clinical study contributed greatly to the success of the research by their exceptional efforts. It was gratifying that in recognition they received an NIH-HEW Group Award for Sustained Superior Service.

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Adult Psychiatry Branch
David A. Hamburg, M. D., Chief

In our Section on Psychosomatic Medicine, we have been investigating some endocrine correlates of mild psychological stress. For the most part, stress studies have centered on critical, high distress, emergency-like conditions. We, too, are pursuing such studies. However, we believe that the mild stresses of ordinary living require investigation also. While endocrine responses under everyday circumstances are likely to be less striking than under emergency conditions, they may, nevertheless, have considerable long-run significance for the human organism. These studies of mild stress, including work on relief of moderate tension, have been conducted with young adult volunteers.

During the past year six groups of normal volunteer subjects have been resident on Ward 4-East for periods of time ranging from 9 to 14 weeks. All of these subjects have been here primarily to participate in psychoendocrinological studies. In general these involve the relations between endocrine function, normal variation in emotional states, and a variety of psychological stresses both induced and occurring spontaneously. A major part of this program of research involved the creation of a fairly normal and standardized living situation within the hospital environment in which a variety of stable psychological and endocrinological observations might be obtained. This is an attempt to form out of the living situation itself a research instrument that might be used for different groups of subjects at different times but be reasonably stable and consistent for comparison of data. We are studying the phenomena of adaptation to this new environment which presents many ambiguities to the entering volunteer. In addition to acting as subjects, the volunteers participate in a variety of work-projects jobs ranging from those of lab technicians to secretarial work. The subjects keep a daily dairy of experiences and thoughts and a daily mood check-list. The head nurse maintains a weekly "problem seminar" directed at specific nursing problems. A well functioning system of routine urine collections has been worked out and nursing staff fills in a weekly set of psychological ratings for each subject. The categories of psychological observations on these lists have been developed with the collaboration of the staff so that consensual validation of categories (e.g., depressed) has been maximized. Frequent discussion and reevaluation helps maintain a high level of inter-observer reliability.

The week of admission to the Clinical Center has provided us with an opportunity for analysis of behavior-hormone relations under mild stress. So far we have studied six groups of normal volunteers, comprising 72 individuals. For most of our normal volunteers, there is an initial preoccupation with NIH, some concern about possible risks, and moderate tension on the day of admission. This is usually followed by a rapid adaptation characterized by active exploration of the new environment, increasing familiarity, encouraging personal relationships, and diminishing tension. For most subjects, this adaptation is largely accomplished by the end of the first week. For five of the six groups, psychological stress was largely absent during the remainder of their stay. There were, of course, individual differences in this respect, but by and large these groups were free of heavy pressures and major uncertainties. However, one group (consisting of 12 students) was brought in under fundamentally different psychological conditions. These were marginal students in a

local university, experiencing serious financial and academic difficulty. For them, the opportunity of living in the Clinical Center for two months while preparing for final examinations was a very favorable circumstance, since it relieved them of financial pressure for the time being. They were, however, under substantial stress as the examinations approached. Interestingly, this group differed sharply from all other groups in patterns of adrenal hormone excretion. Whereas all five other groups showed diminishing excretion of corticosteroids and catechol amines during the initial week in the Clinical Center, this group went up sharply as soon as the students returned to school (after a one-day orientation at NIH) and remained consistently high thereafter. We were also able to get some remarkable data during final examinations on additional endocrine variables, especially estrogen and androgen excretion.

In the past studies of the endocrinological effects of environmental stimulation have almost invariably focused upon the ability of a particular situation to bring about an increase in the circulating levels of certain hormones. Little or no attention has been paid to situations which may consistently lower such endocrine levels. In our Section on Psychosomatic Medicine, we have been attempting to develop experimentally controllable situations of mild stress, and have discovered several conditions which led to the lowering of plasma hydrocortisone concentrations.

Using young (18-25 years) normal volunteer adults of both sexes who spend several months living on the wards at the Clinical Center of the National Institutes of Health, attempts were made to determine if the showing in a group situation of certain selected commercial movies judged to be emotionally "arousing" could bring about consistent increases in plasma hydrocortisone concentrations. As control films, several Disney nature films were also shown. Bloods were drawn from the subjects prior to the showing of the films and immediately afterwards. In addition, self-assessment of mood was obtained from each subject by a modification of the Nowils-Green adjective check list before and after the showing of the films.

In order to control for the showing of either arousing or bland films, a second group of all young adult males had, in addition, bloods drawn during a comparable control period during which time the subjects followed their usual activities on the ward. In order to assess the effects of the possibly mild stressful situations of sustained attention to a long series of visual stimuli in order to respond differentially to them, a group of young adult male subjects were run on the Continuous-Performance Technique developed at NIMH. Bloods were drawn prior to and after each subject was run on the

task. In order to replicate and expand upon the work of Persky, young normal adult subjects were placed in a hypnotic trance after which a particular emotion or emotionally arousing situation was suggested to them. Again bloods were drawn prior to the trance, after the induced trance, and after the presumably emotion-inducing hypnotic suggestion.

The difference in the mean pre-to-post-film changes in plasma hydrocortisone concentration for "bland" vs. "arousing" films corresponds to what might be expected from the nature of the stimulus.

For those subjects for whom control levels were also obtained, there is again a drop in level during the showing of bland films, with only a slight increase in levels during the showing to "arousing" films. The control period shows a drop that is appropriate in terms of diurnal cycle. Contrary to expectations, the subjects run on the Continuous-Performance-Technique also showed a drop in the levels of plasma hydrocortisone. As with Persky's findings, the induction of the hypnotic trance itself reduced the level of plasma hydrocortisone. Also, this effect seems to be stronger than that resulting from assumed emotionally arousing suggestions.

The three stimulus situations which have brought about the lowering of plasma hydrocortisone levels, while different in many respects, do have three major elements in common: (1) The experimental situations, per se, presents to the subjects bland, non-noxious stimulation. (2) The experimental stimulus is such that there results a narrowing of the subjects' attention away from other possibly stressful stimuli of either external or internal origin. (3) The subjects' anticipation of the experiment may serve as a stressor to bring about a rise in the hormone levels prior to the beginning of the experiment. This rise due to anticipation tends to predispose toward lowering the levels during the experiment itself. This may be due to an interaction of a physiological rebound phenomenon and of feelings of subjective relief at the blandness of the situation.

In any event, these findings call attention to psychological conditions under which adrenal hormone levels may be diminished - as well as the more familiar distress conditions under which these levels are elevated.

In the latter part of the year we began three new major stress studies in the neuroendocrine field. The primary stimulus for these studies is our ability to measure several additional hormones: (1) urinary excretion of aldosterone, androgens, and estrogens; (2) blood levels of butanol-extractable iodine as an index of thyroid function. We are interested

in determining whether these hormones will be affected under conditions that have already been shown to be associated with elevated blood levels and urinary excretion of hydrocortisone, epinephrine, and norepinephrine.

The first of these major stress studies is being done through the cooperation of Dr. Gordon Zubrod and his staff in the National Cancer Institute. Dr. Stanford Friedman and associates are doing a study of coping behavior in parents of leukemic children, making serial hormone measurement in patients admitted to our unit for disturbed college students. Similarly, the third study, under the leadership of Dr. William Bunney, involves serial hormone measurement in patients admitted to the Clinical Center because of severe depressive reactions. In the latter two studies, the investigators are working closely with nursing staff to develop systematic observational techniques for rating of behavioral variables.

In most of our psychosomatic research, we are collaborating very closely with the Department of Neuroendocrinology in the Walter Reed Army Institute of Research under Dr. John Mason. Similarly, Dr. Joseph Handlon of the Laboratory of Psychology has been an active collaborator in most of these studies. Also, in several recent projects we have been collaborating with members of the Laboratory of Clinical Science: Dr. Philippe Cardon and Peter Mueller in measuring free fatty acids in relation to emotional distress; and Dr. Roger McDonald and Mrs. Virginia Weise in measuring VMA as an index of adrenomedullary function in depressed patients.

In striking contrast to the apparent importance of sleep and dreaming in human life is the dearth of established knowledge concerning these phenomena. Far from understanding the nature of their psycho-physiological functions, we are lacking even in adequate physiological description of them. It is evident that sleep is not a uniform state from hour to hour in the same night, from night to night in the same individual, or from one individual to another. There is reason to believe that the same is true of the physiological substrate and of the subjective experience of dreaming. Yet the parameters of such variability have yet to be conceptualized and made amenable to measurement. Only then will it be possible to make quantitative studies of sleep and dreaming in relation to the organismic economy. In view of the well known and apparently universal association of disturbed sleep and mental illness, it seems reasonable that attempts to define and quantify the parameters of sleep might eventually lead to important clinical applications.

Dr. Frederick Snyder is investigating physiological and psychological concomitants of sleep and dreaming in an effort to further define and quantify their parameters. In its present phase the project takes the form of a series of small scale, hypothesis-seeking, exploratory studies. All-night records of electroencephalographic, electoculographic, and various other physiological measures, such as respiration, heart rate, plethysmogram, and skin temperature are obtained from sleeping subjects. Details of the procedure have varied among the subprojects through which the study has progressed. For some purposes the recording has been done without disturbance of the subjects' sleep, and for other purposes subjects are systematically awakened by means of graded sound stimuli, at which time they attempt to describe their subjective experience prior to awakening, including whatever dream narratives they can recall. The subjects employed have been normal volunteer controls.

Three types of observations reported by other investigators have been repeated and essentially substantiated: (a) Dream recall is associated with a particular pattern of electroencephalographic and eye movements. (b) There is a regular and invariable recurrence of this physiological pattern three to five times in each night of sleep, taking up an average of 20% of the total sleep time. (c) Interrruption of sleep at the onset of this pattern over a series of consecutive nights leads to a progressive increase in "dream attempts," and the nightly "dream time" is markedly elevated for several nights after the conclusion of the "dream deprivation" period. Several aspects of these phenomena which had not been mentioned in previous reports were noted: (a) A high degree of variability was found in the incidence and vividness of dream recall among subjects, in the same subject from night to night, and over the several dream periods of a given night. (b) There is a considerable range in the percentage of sleep time taken up by "dream sleep," to some extent apparently the expression of individual differences, but to a larger extent taking the form of night-to-night variation in the same subject. An attempt to account for some of the variability in percentage "dream time" through a hypothesized correlation with 17-hydroxycorticosterone levels was not supported. We have further sought physiological parameters of "dream sleep" which would relate to the vividness of dream recall. It was considered feasible to combine this objective with that of a reexamination of the question of sleep "depth." To these ends two additional facets have been explored: (a) Auditory thresholds for awakening and for signs of physiological arousal short of awakening have been obtained during various EEG stages of sleep, and in connection with the subjects' rating of the vividness of his dream memories. In keeping with the reports of previous studies, the auditory thresholds revealed a fairly predictable relationship between

EEG patterns and the intensity of stimulus required for awakening outside of the "dream sleep" periods. It was noted, however, that this relationship was a relative one, with considerable variation in the absolute levels of stimulus required among subjects, or in the same subject under different conditions of "sleep need." Hence, it appears that the EEG pattern is not an absolute index of sleep "depth" as defined in terms of arousal thresholds. Within the periods of "dreaming sleep" the intensity of awakening-stimulus was extremely variable, with no constant relationship to thresholds required during other EEG stages, nor to the vividness of dream recall. (b) Physiological variables other than the EEG and eye movements have been monitored in the hope that they would provide indices which would relate to the vividness of dream recall, or to the depth of sleep as determined by arousal thresholds. Thus far these have included heart rate, respiration, plethysmogram, and skin temperature. This resulted in the finding that all of these measures tend to distinguish between "dreaming sleep" and "dreamless sleep," particularly in terms of the much higher degree of minute-to-minute variability of the measure during dreaming. This is especially striking with regard to the variability of respiratory rhythm. Early results are quite encouraging that this measure may relate to the vividness of dream recall. If further work bears this out, we will feel justified in postulating a parameter of "dream intensity." In relation to sleep depth, each of the autonomic measures is at least roughly related to the EEG stages of sleep. Whether any of them might be a better absolute index of sleep "depth," as measured by arousal thresholds, remains to be studied.

The Field Study Group, under the leadership of Dr. Earle Silber, has been concerned with a naturalistic study of 20 students in the process of transition from high school to college. Our aim is to learn about some of the patterns of problem-solving in late adolescence. By the fall of last year we had selected 20 students from the senior class at the Bethesda-Chevy Chase High School and had completed a series of interviews with them while they were in high school. In addition, we had interviewed their parents, and all of the students in the project had been given a special projective test constructed by Dr. George Coelho and Dr. Silber. This test, patterned after the Thematic Apperception Test, was designed to elicit characteristic modes of dealing with certain potentially stressful situations in college. In the early fall, staff members who had interviewed the students in high school visited them at their respective colleges. In this interview we obtained data about the early weeks of college, the academic work, the experience with friends, roommates, dating, group activities, relationships with parents, impact of new values, satisfaction with college, expansion of new interests, and particular problem areas for the student. In addition, we toured the college

campus with the student as a way of getting a view of the college through the student's eyes. We next met with the students when they visited home during the Christmas vacation. At this time the same areas mentioned in the original college interview were pursued, as well as focusing on current interactions between the student and his family while he was home. During the Christmas vacation, the students were also again asked to take the projective test, which we have referred to as the Students' Thematic Apperception Test.

In the early part of this year a second interview was conducted with the parents by Mrs. Elizabeth Murphey. This interview was focused on the parents' perception of any change in the student and their response to these changes. In addition, we asked about any changes in goals that had been made by the student and the parents' response to this. We also obtained information about the parents' own education and explored with the parents their awareness of what contributed to certain assets or particular coping mechanisms in their children.

The students were seen again when they visited home for their spring school vacation. We continued following up all of the areas that were explored in the early interviews and we were also interested at that time in any change in their feeling about home and their parents following the Christmas vacation.

Students were seen after they had returned home from college in the early part of summer. We again pursued the topics covered in previous interviews with them; in addition, we heard about their plans for summer jobs, discussed the management of finances, and had the student view for us in retrospect some of the important tasks in the transition they experiences and how they were handled.

New pictures were designed for the Students' Thematic Apperception Test and students were again tested in the early part of June.

The summer months were used to conduct a series of joint interviews with the student and his parents. The purpose of this interview was to review with the student and his parents his transition to college from the point of view of the total family experience. These interviews were viewed also as an opportunity to make observations directly about patterns of family interaction.

Now that the data collection is completed, we are in the process of analyzing our material. We plan to maintain contact with each of the students in the project and to see them once a year until the completion of their college experience. We have already reviewed material related to the decision to go to college and factors involved in a choice of college by our students. We have been able to describe certain cultural forces which played a decisive role in directing them toward college. These students internalized an expectation that they would go to college and did not make a conscious decision about going to college. This was related to their family's socio-economic status and the role that education played in the social mobility of their family. In addition, the high school peer culture reinforces the trend toward college. Our students were active in using environmental resources to learn about colleges. The process of selection involved the student's assessing his potential "fit" with particular colleges; that is, a simultaneous process of self-assessment along with an assessment of the college. The parents were active in the selection process, and they were explicit for the most part about their expectations and preferences, at the same time granting a good deal of freedom to the student in making a choice of college. When the student took a position contrary to the parents, the parents were able to accept this without it disrupting their relationship with the student.

We have also examined the coping mechanisms of our students during the time they were in high school, anticipating the change to college. We have been able to define certain personality attributes which would facilitate an active involvement in the tasks of the transition. Our students tend to value new experience, tend toward activity in facing new situations, and derive a good deal of pleasure in the sense of mastery of challenge. In addition, there were more specific mechanisms which could be viewed from the point of view of the student's developing and maintaining a self-image as adequate to the perceived requirements of the new situation. We have observed a number of mechanisms, such as: reference to analogous past experiences, reference to a present self-image, learning about the new situation in advance, role rehearsal, group identification, lowering the level of aspiration, and selectively perceiving encouraging elements in the new situation. In addition, our students were effective in maintaining distress within manageable limits. They viewed concerns that they had about college as being shared by others; some attempted to make their concerns seem desirable; they were active in dealing with issues that they felt they might have some concern about in the future; and finally, they used fantasy rehearsal as a way of dealing with some future contingencies in the college situation.

Certain characteristics of the parents of the students in the Field Study Group have been described. The parents fell roughly into three groups. One group was composed of two families we were not able to interview; in one of these the mother had been psychotic, and in the other there was severe marital conflict. A second group of ten families were similar enough in their characteristics to be considered as a group. Four other families presented exceptions in certain areas. We were impressed with the range of patterning that was compatible with effective functioning in the student. Among the ten families that seemed more homogenous as a group, we could describe such characteristics as: a stability and clarity of values, a persistence and complementarity of roles in the family, the parents' acceptance of their children, the parents' self-acceptance, parents' encouragement and endorsement of the students' autonomy, confidence in the students' abilities, directness in communication and the parents' ability to perceive the students' assets.

At the present time we have completed a unit of analysis concerning the formation of friendships at college. We have been able to describe distinct phases in the pattern of friendships at college. Following an initial, almost indiscriminate, reaching out, there is a later selectivity and sifting based on common interests. The formation of friendships is an important vehicle in providing opportunities for further self-awareness, learning, exploration of new role possibilities. They provide an important sense of belonging, support at moments of crisis, and opportunities for intellectual stimulation. We are planning also to review material about the students' dating experiences and attitudes about sex and marriage. In addition, we will examine how the students dealt with the academic demands and new values at college.

Dr. Coelho has recently completed a report on the development of the Student Thematic Apperception Test. It includes the following material:

1. A description of the STAT instrument and rationale for its use as a projective device in the pre-diagnostic assessment of freshman coping behavior.

2. The operational definitions of three categories constructed for the analysis of STAT stories with respect to the variable, competence in problem-solving during the freshman transition in college. These rating categories are as follows: S, denoting the presence of a resolution in the story; A, denoting active efforts involved in effecting a resolution; F, denoting the presence of a favorable resolution in the story.

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3. Presentation of quantitative results based on comparisons of STAT protocols of three groups of freshmen: 10 students from the Field Group who were identified as exceptionally competent independently on the basis of interview data collected from the students' spring term of the senior year of high school and the fall term of their freshman year in college; 10 ward patients hospitalized in the Clinical Center for psychological difficulties experienced in their freshman year; 10 University of Maryland volunteers selected from an advanced freshman English section.

a) Two gross indices of competence potential were derived from the preliminary results: an optimism index and an effectance index which differentiate between the competence levels, as defined, of the normal and patient groups of freshman subjects.

b) An analysis of variance was carried out to test the levels of the group profiles and the shapes of the group profiles. The results show, on all three categories, significant differences between the competence levels of both the normal groups on one hand and the ward patients on the other. The differences between the Field Group and the University of Maryland freshmen are not statistically significant for A; they are statistically significant for F, but not practically significant.

c) While the level differences are generally parallel between both of the normal groups on one hand and the ward group on the other, the biggest discriminators among the stories are Nos. 7, 9, 10, and 11 (namely, in the scenes -- working to finish final exam under pressure of time (7), dealing with double date situation (9), calling home (10), day dreaming alone (11).

d) A comparison of the STAT protocols of Field Group subjects tested three months before and three months after college entrance shows negligible differences in total positive ratings on any of the three categories S, A, F.

e) A qualitative analysis is under way to investigate activity styles, resolution strategy, and hero imagery in the STAT protocols of the normal and patient groups of freshman subjects.

Dr. Coelho, Dr. Fredric Solomon, and Dr. Thomas Lewis have developed a group interview technique, using a small group of Maryland freshmen as informants, to explore the salience, intensity, and tempo of new environmental pressures experienced

by freshmen. An observational and recording procedure was also developed for analyzing the content of the group interviews without the use of tape recordings. The investigators met with a small volunteer group from an advanced section of freshman English in one of the conference rooms of the Student Union of the University of Maryland. The arrangements were completed through the cooperation of Dean James Borrison. Our group interview data are based on the responses of a core group of five students, interviewed over seven sessions during their freshman year, the group size fluctuating from four to eight.

In addition to these data from Maryland University freshmen, comparative data were obtained, through the group interview method, on two other freshman groups.

1. Eight ward patients who were hospitalized in the Clinical Center, were interviewed over six sessions of one and a half hours each in an area apart from the ward unit, to emphasize the research focus of the group interview as distinct from group therapy.

2. Four freshmen from among the Bennington College normal volunteers were interviewed for five sessions of one and a half hour's duration each.

The following sets of data are now available:

1. An indexed table of contents showing topical areas of high salience, discussed by these three group of subjects; 2. a narrative account of the group discussions with section headings to illustrate the variety of topical areas; and 3. a summary of the highlights of the group interviews with special attention to comparative observations from the three groups of subjects.

An exploratory predictive assessment of freshman coping behavior at the University of Maryland is now being undertaken by Dr. Coelho, Dr. Solomon, Dr. Carl Wolff, using a sample of dormitory residents who were selected on the basis of Hi and Lo STAT ratings.

The specific research aims of this Maryland freshman study are:

1. To clarify in a predictive way the correspondence between fantasied coping behavior based on STAT performance and behavioral competence based on focused interview data collected during the second week of November 1960.

2. To explore the early coping behavior patterns of Maryland dormitory residents engaged in dealing with their new freshman situation.

A sample of 40 dormitory residents was selected from the total number of 350 freshmen to whom the STAT was administered in August 1960, during the pre-college orientation program. The total group of 350 incoming freshmen were tested during the orientation program period, representing about one-fifth of the total number of students who attended the pre-college orientation program on the Maryland campus in August. An interview guide focussing on specific questions in the following areas had been prepared:

1. Meeting of academic tasks, interest in course work, planning of tentative major and vocational directions.

2. Handling of separation from home, communication and visiting patterns with members of the family.

3. Initiation of friendships and involvement in group activities.

4. Experiences in the dormitory situation and with the roommate.

We have also approached the study of personality development in late adolescence by selecting a widespread and significant task of that developmental phase and studying individuals who manifest disturbance in their efforts to accomplish this task. The task we have selected is that posed by the requirements of the transition from high school to college. Under the leadership of Dr. Roger Shapiro, we have accepted as patients for our study young people who have had sufficient emotional difficulty during their freshman year at college to make it necessary that they drop out of school. We have conceived of the adjustment to college as containing many of the developmental tasks of late adolescence, which make demands upon the adaptive capacities of the individual in a number of areas. Among these tasks are: separation from parents and living away from the family for a prolonged period of time; living primarily with peers and having more significant relationships with peers; the demands of increasingly intense and mature patterns of sexual expression; the increasing intellectual demands of college work; an increasing requirement for decisions relating to vocational choice. We want to determine what current and past social experience interacts with the individual potentialities, to encourage the adaptive capacity of the individual in his mastery of the tasks of this phase, conceptualized by Erikson in their most generalized form as the achievement of a sense of ego identity. We want to understand what is lacking or inhibiting in the particular life

experience of the individuals we study, both current and in the past, to interfere with the realization of their potentialities in late adolescence. Finally, we want to utilize our therapeutic program in a way which will help us to understand what aspects of current social experience can encourage realization of potentialities previously interfered with and allow for further personality development. We are concentrating our investigative efforts in two broad areas in our attempts to answer these questions. We are studying the recent situation in which the patient experienced acute difficulty, the developmental task with which he was confronted in college; and we are studying the family experience of the individual.

Our efforts to study the college experience of our patients has taken three major forms. Each of our patients is interviewed by one of the investigators in a series of research interviews which follow a schedule of areas of particular interest to us. Questions are asked in the following areas: What was involved in the decision to go to college; in the emotional preparation for college; in the initial adjustment to college; in friendship formation in college; in the reaction to the academic challenge; in other areas of difficulty in adjustment; in various reactions to these difficulties; in the crises and the departure from school. A second source of information about the college experience is contained in the picture obtained in psychotherapeutic work with the patient of what his college experience was. This is organized and written up by the therapist in a form covering the same areas of interest as the research interviews so that they can be compared. A third source of information about the college experience is a visit made by one of our investigators to the college in which the patient had difficulty, to interview friends, teachers, and advisors of the patient in an effort to gain another vantage point for viewing the nature of the psychosocial environment with which the patient had to deal, adaptive efforts he made in the situation, and the nature of the relationships he formed. The patient's picture of these adaptive efforts and relationships is compared with the picture of those who knew him.

Our effort to study the family experience of the patient has in the past six months resulted in our utilizing the study of family sessions involving the patient, his parents, an adolescent sibling if available, the therapist of the patient, and the social worker. These sessions are held for one hour weekly and are observed by two investigators. They are integrated into our therapy program, which also includes two individual sessions a week for the parents with the social worker, and two sessions of group therapy per week for the patients.

We attempt to utilize interviews when family interaction can be observed, to shed light on the identity question in the following way: We pay particular attention to the interaction between parents and patient which gave some indication of the way in which the parents overtly and covertly identify the patient and the way in which he overtly and covertly identifies the parents. If we can see demonstrated relatively rigid and enduring delineations of the patient by his parents, which make for inflexibility in his sense of identity and anxiety over the changes in the concept of himself which the developmental phase requires, we will understand more of what contributes to pathological outcome in the period of identity crisis. We look also for evidence of inflexibility and stereotyped expectation on the part of the patient in the manner in which he delineates his parents, and undefensively keeps them in stereotyped and rigid roles. With this identity question as the central focus of our research interest in the family sessions, we report on this aspect of the interaction in two ways. The therapist makes it a part of his summary of the interview; and observers follow each interview from this point of view rating on a prepared flow sheet sequences in the interview which reveal parental expectations of the patient and patient's expectations of the parents, delineations back and forth of what they can allow into their concept of the other. This includes their conscious statements about the other person; it also includes affective behavior toward the other person from which unspoken or unconscious attitudes can be inferred. We have two observers recording independent impressions in an effort to arrive at reasonably objective findings.

This investigation into problems in the personality development of the late adolescent has been in progress since January 1959. In these two years we have hospitalized nineteen college students, predominantly freshmen, who were in sufficient emotional difficulty to make it advisable that they leave school. Interviews with these students about their college experience allow generalizations to be made in a variety of areas. We have summarized the data from interviews of ten of these students under the following headings, and are now analyzing the remainder along these lines: 1. Attitudes toward new situations and change; 2. Manner of arriving at the college decision; 3. Dating and sexuality; 4. Order, organization and control; 5. Friendship patterns at college; and 6. Grades, studies, intellectual achievement as a problem.

In connection with the study of freshman college students whose emotional difficulties prevented them from continuing with their college courses, it seemed advisable to develop a psychological instrument which might be of assistance in exploring the personality assets and liabilities of students with specific

reference to their capacity for adjustment to their peers and to members of the hospital staff. We wished to set down in systematic and roughly quantitative form the observations of ward staff on personal relations of the student-patients. We are comparing these with the observations of another ward staff, using the same instrument, on normal volunteer college students. The development of this instrument was undertaken by Dr. Harold Greenberg and Dr. Sheldon Korchin.

Two sources were used in an initial effort to develop categories germane to an evaluation of the personality assets and liabilities of hospitalized college students: 1. Recorded interviews with the parents of these students in which the parents were asked for their assessment of their child's personality assets and liabilities; 2. Opinions of the nursing staff in this regard (favorable or unfavorable qualities which seemed of special import as staff members observed the student's relationship with them).

Using these data, nine general categories of "ego function" were developed which would serve as a basis for a more detailed evaluation of personality assets. Each of the nine categories was then subdivided into specific components. The nine categories were as follows: 1. Degree of Initiative, Activity, and Thought Process; 2. Socialization; 3. Work Goals, Productivity; 4. The Capacity for Effectiveness; 5. Sense of Identity - the Integrity of the Self; 6. Dependency, Independency; 7. Flexibility; 8. Impulsivity; and 9. Character Assets and Liabilities.

In all, a total of 116 statements referable to the above categories was developed as a set of rating scales.

During the last several years, under the leadership of Dr. Lyman Wynne, the Section on Family Studies has been collecting a considerable body of data on, and has formulated preliminary hypotheses about, the place of family relationship patterns in schizophrenic illness compared to nonschizophrenic psychiatric illness. During 1960 the Section decided that the process of data collection and hypothesis formulation had proceeded sufficiently far so that it is now appropriate to shift the primary emphasis from clinical exploration of family patterns to a more comprehensive review and description of the available material and to a systematic evaluation of certain hypotheses in the light of this data. The shift to the latter emphasis is at present underway and it is expected that it will be possible to report substantive findings during the coming year. The present summary will not attempt to anticipate the statement of findings and conclusions that are emerging, but will be limited to an outline of the current trends in the work of the Family Studies program.

1. In order to create more time for writing and research evaluation of the material which has accumulated, the Section has reduced the clinical case load of the families being seen. However, to add at least slowly to the number of families studied and to keep the writing and research evaluation invigorated with currently "live" family observations, the Section is continuing to see a small number of families clinically in family psychotherapy and family art therapy, with certain other families observed or treated jointly with Dr. Shapiro and members of the college student Personality Growth program.

2. The Section is planning extensive, detailed, naturalistic descriptions of the family data in order to characterize as vividly as possible certain features of the family processes which have been observed. Family therapy sessions have now been held with 27 families one to three times weekly for periods of six weeks to almost three years. All sessions have been tape recorded and most sessions, since September 1959, have been directly observed through a one-way mirror. Because conjoint exploratory therapy with families, especially with the families of schizophrenics, is a new and generally unknown approach in the psychiatric profession as a whole and because it taps details of schizophrenic family interaction not previously available to scrutiny, it seems highly desirable that our extensive experience be reported descriptively and naturalistically.

Although comprehensive descriptive reports remain as a current task, during the past year members of the Section have presented several short descriptive papers at various professional meetings on the subjects of: sibling-patient comparison -- the characteristics of the psychiatrically disturbed offspring compared with apparently normal siblings; clinical observations supporting the hypothesis that schizophrenic thought disorder may be a learned aspect of family life; observations on the nature of the experience of therapists while working intensively with the families of schizophrenics, as providing clues to intrafamilial experience; the use of family art therapy for understanding certain aspects, expecially non-verbal features, of family interaction; and a consideration of certain over-all structural characteristics of family organization, especially intrafamilial alignments and splits, as a method of focusing on certain homeostatic family processes.

3. The Section is engaged in the construction of a comprehensive theory of psychological developments within the family setting. Such theory construction is necessary in order to distinguish the crucial from the trivial hypotheses about family relationships. It is hoped that the formulation undergoing development will facilitate interpretation of these underlying, genotypical features of family life which are especially pertinent to certain crucial aspects of schizophrenic

impairment, especially the thought disorder and the incapacity to maintain major sets.

4. A central concern in the work of the Section is the development of two kinds of systematic comparison studies: first, comparison of families having schizophrenic versus nonschizophrenic psychiatrically ill offspring; second, the comparison of siblings, schizophrenic and nonschizophrenic, within the same family.

Data from 32 families are now available for these comparison studies. During the past three years families have been specifically selected with these comparison studies in mind. The criteria involved minimizing all presenting differences between the families except one: the presence of a schizophrenic versus a nonschizophrenic (but psychiatrically ill and hospitalized) young adult offspring. An effort has been made to match families in terms of social class and class-related values; each family has consisted of the two biological parents, the hospitalized offspring, and at least one offspring who is not overtly disturbed psychiatrically.

In order to correlate various aspects of family patterns with the degree of schizophrenic illness in the offspring, it has been necessary to rank-order the psychiatrically disturbed offspring along a dimension of degree of schizophrenic illness or tendency. During the past year a variety of ways of specifying the dimensions of "schizophrenicness" were empirically tried. A modified paired-comparisons method was used to make consistent rank-order ratings of all 37 patients seen in the program thus far. (Two families had multiple-birth patient-offspring, so the number of primary patients outnumber the families.) Dr. Margaret Thaler Singer, consultant to the project, similarly ranked 22 of the patients whose psychological tests she had seen. The clinical ranking and her ranking on the basis of the psychological tests she had seen. The clinical ranking and her ranking on the basis of the psychological tests proved to be almost identical. Thus, a satisfactory rank-ordering of the presenting patients in now available for use in the comparison studies of the families.

Dr. Singer has continued with her studies in which she matches "blind" the presenting patients with their families. Given the psychological test protocols of the family members except for the tests of the presenting patients, Dr. Singer has been able to make remarkably accurate predictions of the schizophrenic or nonschizophrenic characterists of the patient family member. Then, looking at the tests of the patient family members, she has attempted to match patient and family "blind," taking 4 to 7 families in a set.

She has now carried out this procedure with 22 families from the Family Studies program. In addition, she has matched 11 schizophrenic patients and families tested by the Yale Family Studies program headed by Dr. Theodore Lidz. Focusing particularly upon the form or style of thinking used within the families, Dr. Singer has been trying to specify criteria upon which she has been able to make her predictions and matchings. The next phase in the work will be to ask other judges to use her criteria to make the same differentiations and matchings "blind." The preliminary success which Dr. Singer has achieved is highly promising confirmatory evidence that the family characteristics of schizophrenics and of nonschizophrenics can in fact be differentiated and these families do have a sub-culture and a system of relations which involves the entire family, with the psychiatrically disturbed offspring constituting an integral part.

A second variety of systematic studies which is underway involves the use of excerpts from family therapy sessions. Several pilot studies have been conducted in which these excerpts are rated along dimensions which are relevant to the question of the connection between family relationship patterns and degree of schizophrenic illness in offspring. Excerpts from the family therapy with 14 families, 7 having a schizophrenic and 7 a nonschizophrenic psychiatrically ill offspring, have been selected for the comparison studies currently being conducted. Thus far excerpts have been selected in which the parents respond to a comment of a therapist and in which there is no indication of the diagnostic characteristics of the offspring. The preliminary results are encouraging with respect to the capacity of the excerpt technique for differentiating successfully the families of schizophrenics and nonschizophrenics.

A complex study being conducted by Mr. George Usdansky using this approach has yielded positive results in an extensive pilot study and is now being verified by rating of the family therapy excerpts made by two outside judges who are unfamiliar with both the hypotheses being tested and the diagnostic identities of the particular families whose excerpts are being used. In this particular study the families have been compared in terms of frequency of occurrence of certain kinds of interpersonal maneuvers which our previous hypotheses indicate may be particularly relevant. Using the rank-order ratings of degree of schizophrenic illness or tendency, it will be possible to compare these independent ratings of the maneuvers used by the parents with the degree of illness of the offspring.

5. As indicated in the annual report of last year, the use of conjoint family therapy as an exploratory research tool has led to a significant by-product: the development of the theory and technique of family therapy, an approach recently

achieving wide recognition as a potentially valuable addition to the therapeutic repertory of psychiatrists. In the extensive use of this approach in the Family Study Section, many observations have been possible about the advantages and limitations, the indications and contraindications for exploratory family therapy. Ideas have been developed about technical problems peculiar to family therapy, about differences in technique of family therapy as compared to both individual and group therapy, and about the therapeutically effective aspects of family therapy. Although the work of the Section is primarily oriented toward untangling the relation of family patterns to schizophrenia, the experience in using exploratory family therapy with the families of schizophrenics has been perhaps more extensive than with any other group in this country and deserves report and discussion in future publications from the standpoint of therapeutic technique.

During the past year a pilot study in mental health counseling was begun, under the leadership of Dr. Margaret Rioch and Dr. Charmian Elkes. This study is exploring ways of alleviating the shortage of trained workers to provide low-cost mental health services. The idea behind the study is that, just as the Public Health nurse can perform many duties with and for patients which free the medical officer for the more difficult tasks requiring greater training, so a corps of workers might be trained in the mental health field to deal with the simpler problems, thereby freeing the psychiatrist to treat the more severely distrubed patients. There are probably many people in the community who have aptitude for this kind of work but are not trained for it. One reservoir of such people consists of married women who around age 40 are looking for a constructive activity outside the home to take place of child rearing. We wish to determine whether such women, if carefully selected, can be trained within two years to perform mental health counseling. In this investigation, the area will be the problems of late adolescence and young adulthood. One of the main reasons for the choice of the particular area is the fact of the other work going on in the Branch with this age group.

Mental health counseling in this context means dealing in a psychotherapeutic manner, through interviewing, with minor to moderately serious emotional disturbances. It does not mean the independent practice of psychotherapy. It is clearly understood by all participants in this project that these counselors will work under supervision and will not be asked to diagnose their clients. Clients will be screened by experienced psychiatrists and the counseling itself will be done under careful supervision by NIMH personnel.

The experiment can be divided into four stages of unequal length: Recruitment, Selection, Training, and Evaluation. The first two have been completed. The third is in process; the fourth is in the planning phase.

In the recruitment stage we wanted to determine whether it would be feasible to locate a substantial number of women interested in taking this kind of training without any financial recompense even though they are told emphatically that it is an experiment with no guarantee of employment afterward. This was amply demonstrated, at least for the Washington area. As a result of about 60 telephone calls to individuals and organizations, and 6 speeches, all of which occurred between mid-April and June 1, 1960, 80 women requested and received application blanks. No application blank was sent out without a ten-minute telephone conversation with the applicant explaining the project and emphasizing the risks. Forty-nine of the blanks were returned, filled out by people who could reasonably be considered as applicants. The response indicates clearly that this kind of program fills a real need felt by women around 40 for appropriate training in an occupation which is especially suited to their capacities.

The selection stage took place between mid-May and June 28, 1960. Criteria for selection were as follows: 1. High general intelligence; 2. psychological perceptiveness about others and undefensive awareness about themselves; 3. integrity; and 4. sufficient emotional maturity to be able to work effectively together and to cope with the stresses of therapeutic work.

The selection procedures included five steps in the following order. Some applicants either fell out or were dropped out at the end of each step so that only 14 arrived at the fifth step. 1. Application blank to be filled out. 2. An autobiography to be written by each applicant of about 1,500 words in which she was asked to describe different stages of her development to be the kind of person she is. 3. A group session which lasted from 9:00 a.m. to 3:00 p.m. The applicants were asked to come to the NIH for these sessions in groups of about 8. They were put through various tasks including interviewing and introducing each other, discussing a topic and arriving at a consensus, discussing a tape-recorded initial interview, and paper and pencil group tests. There were always at least two observers, usually three. 4. Individual tests and individual interviews. The tests were the Rorschach, a modified and abbreviated TAT, and three items of the Wechsler-Bellevue Scale. Each candidate had two 1-1/2 hour individual interviews, each with one of the two with a different interviewer. 5. A final group session in small groups of about

seven in each and a final individual interview, usually with a new interviewer. On the basis of these procedures, eight trainees were chosen by a consensus of all those who had been engaged in the selection procedures.

It is the opinion of those who have been in contact with these candidates so far in the training stage of the experiment that they do have aptitude for the training and that they do demonstrate the qualities sought for in the selection procedures. The selectors are for the most part the teachers in the training program. This seems to ensure the selection of candidates with whom communication is easy for the teachers, who are themselves therapists, and who have apparently chosen a group of candidates whose values and ways of thinking are similar to their own. The limitation in this from the viewpoint of research into the process of selection is that there can be no answer to the question whether the applicants who were not selected might have turned out as well as or better than the ones selected. The system perpetuates the values and qualities of people who are at preent successful therapists, but does not investigate the possibilities of using other values and qualities.

However that may be, there is general satisfaction among the teachers in this pilot project with the results of the selection. Work is still in progress to determine to what extent the psychological tests should be considered a necessary part of the procedure. But the group sessions, followed by individual procedures for those not weeded out by the group sessions, were satisfactory methods for assessing the qualities of the applicants and can be recommended for the selection of trainees in programs having to do with interpersonal relations.

The training stage of the study has been in progress since September 12, 1960. The candidates have been asked to be prepared to schedule flexibly 20 hours a week of work outside their homes and in addition to do some reading which can be done at home. This permits the women to cover their domestic responsibilities and still to participate in an intensive, very practical, on-the-job course of training.

During the first few weeks the candidates were given an orientation and a series of lectures by various members of the NIMH staff from within and without the Branch. In the third week they began to settle into a regular schedule. This includes at the present time the following 9 items of which No. 8 is considered the most important. 1. A lecture course, two hours a week, on Personality Development, by Dr. Blanche Sweet. 2. A clinical seminar, two hours a week, by Dr. Charmian Elkes. 3. A clinical seminar, two hours every other week, by Dr. Margaret Rioch. 4. A seminar devoted to a discussion of reading

material, two hours every other week, by Dr. Margaret Rioch. 5. A seminar on Family Dynamics, two hours a week, by Dr. Arden Flint. 6. A supervisory seminar in groups of four, two hours a week, by Drs. Elkes and Rioch. 7. Observation of live interviews by experienced therapists, about two hours a week. 8. Interviews by the candidates themselves with the normal control subjects at the various Institutes of NIH, about three hours a week. These are always tape recorded and supervised by Drs. Elkes and Rioch. They are listened to and written up by the candidates themselves. 9. Placements in one of the following community agencies, four hours a week: D. C. Juvenile Court, Montgomery County Juvenile Court, U. S. Probation Service, Family Service Agency of Montgomery County, and NIMH Study Center at Langley Park. In these agencies the candidates have observed interviews and in most of them they are now taking active part in the work of the agency by interviewing themselves under the supervision of experienced agency workers.

DEVELOPMENTAL PATTERNS IN THE YOUNG FAMILY: ANNUAL REPORT ON THE FIRST YEAR OF A LONGITUDINAL STUDY

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PROGRAM SUMMARY: 1960

The Study of Newlyweds

I Aim

II Hypotheses

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Appendix

Child Research Branch
D. Wells Goodrich, M.D., Acting Chief

PROGRAM SUMMARY: 1960

The general aim of the present Child Research Branch program, which was initiated at the beginning of fiscal year 1960, is to develop a systematic longitudinal program of interlocking projects to explore the initial stages of family formation in volunteer subjects, subjects not receiving psychiatric treatment. Three research problems are central: 1) the developmental channels of two separate systems of behavior in the firstborn infant from birth to age $2\frac{1}{2}$ years; 2) the development of the marital bond in various types of married couples from the stage of being newlyweds (they are studied at three to four months of marriage) to the stage of initial parenthood; and 3) the relationship of the initial interaction patterns, established between the new parents and their firstborn child in the first few weeks of life, to the infant's particular behavior pattern and to the marital type.

In order to implement this general aim, three projects have been under way over the past year. Dr. Richard Q. Bell has initiated his third study (Project No. MCR(C)11) of neonatal behavior characteristics, refining earlier measures of oral integration and of skin sensitivity in the three to four day old neonate. These infants are being studied in families who plan to continue to reside in Montgomery County (unlike the subjects for his previous two studies, who were infants of U.S. Navy transient families). The observations are carried out at the Suburban Hospital. The establishment of this study at the hospital in the spring of 1960 required extensive administrative efforts in order to secure the full cooperation of the staff of this hospital. To date 50 such infants have been processed; the plan is to follow up these infants as $2\frac{1}{2}$ year olds in the Nursery School observation situation between 1962 and 1963.

In the second project carried out this past year, Dr. Bell has developed a set of time-sampling observational methods to apply to the adaptation of $2\frac{1}{2}$ year olds to a nursery school experience of four weeks duration (see Project No. MCR(C)10). In preliminary data gathered on a group of 40 males it appears that there may be a significant correlation between these observed patterns of $2\frac{1}{2}$ year old behavior and the retrospectively parent-reported neonatal behavior patterns in this sample. It will remain for the first-mentioned study, however, to show that this correlation (if it is confirmed during the next year's work on females) is not derived from a distortion based upon faulty parental recall.

The third project of the Child Research Branch is the study of newlywed couples. Work during the past year has involved the development of methods in a neglected area of developmental research. During this prepilot phase, 40 couples have been assessed in complimentary ways. Based upon this experience, the exploratory foci for the study have been extended considerably beyond that envisaged a year ago (see footnote 2a., below). During 1961 a pilot study involving an intensive assessment of 40 new couples will be carried out, permitting the testing of a few hypotheses and the more rigorous exploration

of the operational relations between various methods now in use and between the variables now being assessed. On the basis of this pilot study it should be possible to initiate a large scale study of approximately 150 couples, as the second cohort of the longitudinal study. (The 40 couples already seen this past year, as well as the 40 additional couples to be seen this coming year will also be followed into the neonatal phase, thus constituting the first prepilot and pilot "cohorts" of the study.)

The overall strategy of this longitudinal program is thus to move from our current position of carrying out three separate projects on newlywed couples, on neonatal infants and on 2½ year olds to an intermediate position of carrying out during 1961-1963 two overlapping projects, the one linking the phase of newlywed marriage to the the neonatal phase and the other linking the neonatal behavior patterns to the 2½ year old behavior patterns. Thereafter we expect to be in a sound position to carry out longitudinal studies linking all three developmental phases on the same subjects. More specifically, the program aims in the future to focus on a small number of theoretically and phenomenologically interrelated variables, studied on large cohorts of families. Intensive studies will be carried out only on a small number of systematically-selected families who will represent theoretically or clinically salient subsamples; these families will provide an opportunity to investigate the totality of family interaction in greater depth, and thus to feed back new information and to suggest needed modifications of hypotheses. Unlike many previous longitudinal studies, the program avoids continuous data-gathering on subjects through time, and concentrates on intensive investigation cross-sectionally at a given developmental phase. No single methodological approach is adopted but rather a combination of interviews, structured and unstructured observational and questionnaire methods is used. The focus of research questions is on both specific variables, for example, the later developmental expressions in the 2½ year old of a neonatal pattern of vigorous effective oral behavior, and on general areas of descriptive data-gathering, for example, the exploration of early marital events affecting the courtship and decision to marry. Since the progress to date in the projects on neonatal behavior (Project No. MCR(C)11) and on 2½ year old behavior (Project No. MCR(C)10) has been adequately summarized in the Annual Project Reports, and since the exploratory nature of the study of newlyweds has made our current activities difficult to communicate in brief form, the remainder of this annual report of the Child Research Branch will be devoted to a more detailed description of the study of newlyweds who serve as the first cohort of the longitudinal study.

THE STUDY OF NEWLYWEDS

I. Aims:

In January 1960, after approximately five months of planning activities by our interdisciplinary Couples Study Planning Group 1/, it was possible to

1/ This group is currently composed of Paul Blank, M.S.W.; John D. Campbell, Ph.D.; Naomi Costello, B.A.; Arden Flint, M.D.; Wells Goodrich, M.D.; Ann Lewis, B.A.; Harold Raush, Ph.D.; and Walter Sceery, M.S.W.

4. The initial triadic adjustment of infant-mother-father during the neonatal period. (This portion of the study will be initiated during the coming year with the pilot study of 40 couples.)

The project is concerned with several specific aspects of family interaction which serve to define the variables and to guide hypotheses about family relationships and developmental changes, including:

1. Feeding and eating as a setting for interpersonal interaction.

2. Affectional physical contact (touching, holding) as a setting for interpersonal interaction.

3. Freedom of expression of affect versus inhibition of affective expression in interpersonal interaction.

4. Modes of marital decision-making in new or problem ("crisis") situations.

5. Marital and parental role activities and perceptions, especially with regard to sexual adjustment, other forms of affectional contact, parental planning activities, feeding-eating activities, housekeeping activities, occupation, socialization activities with friends, and relationships with close family members (in-laws).

With reference to these general foci and specific aspects of family development, the project is studying both relationships (e.g. the couple as a unit, the mother-infant dyad as a unit, etc.) and attributes of individuals, (e.g. of three-months' married husbands, of four day old infants, etc.) as illustrated in the diagram on the next page.

It will not come as a surprise to anyone familiar with the vicissitudes of scientific endeavor to learn that between January and December 1960 the project staff revised many of the initial plans. Between January and May, 9 couples were studied in an informal exploratory way. Since June, 31 couples have been assessed in a pre-pilot project by means of joint home interviews, individual tape recorded interviews, the color-matching test, the improvisations, and a set of questionnaires. As a result of this experience it has been possible to standardize the color -matching test, the questionnaires, and the improvisations procedures, all of which are essentially new and devised specifically for this project.

The development of theoretically meaningful, semi-structured interview techniques has, however, presented considerably more methodological, theoretical and clinical problems than had been anticipated. By September we had to face the fact that, while we had developed and tried out four separate interview schedules during the summer, none met the requirements of the project. During this fall, the major effort has been to develop a clinically meaningful, standard and semi-structured interview form which will cover most of the areas of theoretical interest to us and also be reliable and suitable for various kinds of statistical analysis. A few couples have been seen since September for the purpose of testing portions of the interview procedure. Also this fall it has been possible to begin preliminary work on data analysis procedures.

During 1961, we anticipate studying 40 couples with the standard procedures which have been developed. This will represent a somewhat more extensive and expensive data-gathering effort on each couple than had been anticipated in the spring of 1960, but it will permit us to examine a large proportion of the phenomena which the planning group had decided would be worth examining. In order to be able to differentiate between changes in the marital relationship associated with simple maturation and changes associated with a specific developmental phase, at points in time (such as pregnancy or the neonatal phase) when the couples are reassessed, a control group of matched couples will be studied who, though married a comparable time, have not yet experienced the phase. The data from these couples will be "mined" intensively, exploring patterns of variables and relationships between theoretically-connected data. The information on these 40 couples will serve as a basis for developing final data analysis procedures.

After these data have been collected, we expect to refine our assessment procedures, selecting only those most promising hypotheses and techniques, and beginning to assess each couple in a more "streamlined" fashion. By this means, after 1961, we expect to be able to increase our rate of assessment of new couples to 15 or 20 per month.

Two other research efforts are planned for 1961 (under the direction of Drs. Harold Raush and Arden Flint); the initiation of a small number of intensive personality studies on individual couples and the execution of a pilot study on the neonatal triad of infant-mother-father. Dr. Richard Bell's current project on the relationships of neonatal behavior characteristics to behavior patterns in the $2\frac{1}{2}$ year old will not be completed before 1963. We anticipate also that it will require two to three years more before a really meaningful integration of the Newlywed Study with the Infants Study can be achieved in operation.

II. Hypotheses:

In our initial plan for the Couples Study, it was stated:

"It is our intention that the couples represent, broadly speaking, the socio-economically middle group of suburban young families. In this sense, the social characteristics serve as control variables. It may be possible to include in the final proposal some examination of three questions of theoretical interest: 1) The relationships between grandparents' child-rearing behaviors around the issues of feeding and affectional contact and these areas of interaction in the new family; 2) The influence of intergenerational conflict, as it may be expressed in contrasting definitions of parental role, upon events in the neonatal period; and 3) The influence of such factors as sibling birth order, temporal spacing of children, number of siblings, major disruptions in early family relationships, etc., in the parental family of orientation upon the neonatal crisis."

The general hypotheses of interest in January 1960 were:

1. "Certain dimensions of the initial marital role relationship, expressed in the setting of affectional contact, will be predictive of aspects

of the mother's contact with her newborn.

2. Certain dimensions of the initial marital role relationship, expressed in the setting of feeding activities, will be predictive of aspects of the mother's feeding of her newborn.

3. Extreme patterns of neonatal oral integration (vigor-and-effectiveness of eating) will influence the interactional events of the neonatal crisis in selected families.

4. Extreme patterns of neonatal skin responsiveness (sensitivity to light touch and temperature change) will influence the interactional events of the neonatal crisis in selected families.

5. The conflictedness of the mother's relationship with the maternal grandmother in settings involving affectional contact or feeding activities will be predictive of aspects of the mother-infant relationship in the neonatal period.

6. Certain social characteristics of the couple's families of orientation, if related to current social characteristics of the marriage, may predict transactional processes in the neonatal family crisis."

Illustrative specific hypotheses of interest to the Planning Group have been as follows:

1. "Parents with low mutual expression of affectional contact, if provided with a highly skin responsive infant, will foster greater bodily tension in neonatal infant-holding situations.

2. Parents with a marital interaction pattern of rigid maternal dominance and paternal passivity in feeding settings will foster greater tension in neonatal mother-child feeding settings than other marital interaction patterns.

3. Infants low on the vigor-and-affectiveness of eating factor, born to passive women (as defined in specific marital settings) will tend to show greater tension during mother-infant feeding activities than will other types of infant-mother pairs.

4. Couples with rigid marital role behavior patterns in the prepregnant phase will tend to show slower stabilization of neonatal mother-child interaction patterns, and more frequent infant disturbances, than couples with more flexible role behavior patterns.

5. Tension in mother and in infant, during neonatal situations of infant feeding and infant holding, will be observably higher in families where the mother-maternal grandmother relationship was conflicted in these areas than in families unconflicted in these respects."

On the basis of our experience during the past year the major questions guiding the current work of the Couples Study have been extended and further

specified. We are now concerned with exploring systematically the patterns of initial adaptation between the newlywed husband and wife, as well as the patterns of individual development of each individual. These patterns, to be described rather briefly below, represent the major interests of the research planning group and have guided the development of our methodology. Formulation of these patterns at this time will serve to guide our initial efforts at data analysis.

In one sense the Couples Study is concerned with dimensions of the newlywed relationship which may be expected to relate to general effectiveness as future parents of a young infant. For example, the pattern of nurturance within the newlywed marital transactions themselves may be expected to bear a set of contingent connections to the nurturance-neglect dimension of the parent-infant relationship later on. The actual pathways of influence for such a general aspect of the initial marital adaptation, however, may not be feasible to specify at this time, or perhaps for a long time to come. These general aspects of the initial marital relationship have been selected for study, for the most part, because they are relevant to two pervasive interests of ours: an interest in the marital career as such, as it changes through time and without regard necessarily to child rearing, and an interest in the impact of these patterns upon several types of infants who may be born to the couple.

In addition to assessing the nurturance-pattern in the newlywed relationship, the project is exploring such general interpersonal patterns as collaborative or non-collaborative modes of decision-making, the shared or non-shared activities[5], the relative salience of various newlywed activities[5] within their values about early family life, the currently-held prospective fantasies about initial parental experience, and the patterns of resolution of marital conflict situations involving either differing perceptions of reality or differing aims or intentions. Within the developmental stage of newlywed marriage, a major task is the mastery of initial sexual adjustment. This adjustment is explored in an individual interview with each spouse. Various forms (see "Structure and Process in the Primary Crises of Personality Development," by W. Goodrich, Feb., 1960) of mastery or failure to master this developmental issue will be described. The connections between these forms of developmental stage mastery and the general patterns outlined above may then be explored. Existing studies do not agree on the rate or form of resolution of initial sexual difficulties. Some reports suggest that sexual adjustment takes place in the course of the first several weeks of marriage, other studies suggest that sexual adjustment is not achieved in the average couple for many years.

In addition, the couple's patterns of marital career development will be explored in a joint interview with husband and wife, focusing upon the

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5/ The activities which are most intensively studied, aside from the sexual area, are housekeeping, feeding, parental planning, general physical affection, socialization with friends, participation with close relatives, and occupational activities.

major change events which took place at their first meeting, through the courtship, the wedding, and the honeymoon, and up to the initial establishment of a separate home life. We seek here a better understanding of major interpersonal influences within the relationship, or major external forces influencing the couple, which have shaped past decisions and marital career changes.

In a more specific sense, the Couples Study is concerned with dimensions of the newlywed relationship which grow out of the Infant Study, i.e., the oral effectiveness and skin sensitivity of the newborn. For example, variables within the Couples Study have been selected because they are assumed to reflect the latent capacity of the couple to respond (at a later date, after the arrival of the firstborn) effectively to a low-drive, low efficiency feeding pattern in an infant. This pattern would only be studied for those couples who receive such an infant, and obviously it would not be assessed routinely as an aspect of marital career development. The patterns which grow out of the Infant Study include also the capacity of the couple to respond to an orally demanding infant, their capacity to respond warmly to the skin-sensitive infant, and their capacity to accept a low-skin-sensitivity infant, without demand that it respond. These rather more specific interests have led us to include in the Couples Study an investigation of patterns of physical contact and of feeding activities in the newlywed marriage, as well as to focus heavily upon the individual history of each spouse with regard to physical affection and feeding activities vis à vis his or her parents while growing up.

Since the general dimension of expressivity or inhibition of affective expression appears to be emerging from the data of the first year's Nursery School observations as possibly related to the infant study variables, we are interested in this dimension as it may appear in the initial marital adjustment of each couple and as it may be reported to have existed for each spouse during his or her earlier parental relationships.

We also will be in a position to examine another set of relationships, namely, the relationships between the image each spouse has of developmental experience with his or her parents and the aforementioned patterns of newlywed adaptation or patterns of family adaptation to the arrival of the newborn. These areas of developmental experience, tapped in the individual interview of each spouse, include patterns of parental availability and nurturance, parental neglect and unavailability, parental behavior in relation to food preparation and family socialization at mealtimes, physical affection with parents and the expression or inhibition of impulses in each spouse's family while she or he was growing up.

III. Method:

The Couples Study uses a combination of interviews, direct observations of marital interaction, and questionnaires.

A. Interviews:

1. An initial two-hour home interview is carried out during which the couple's commitment to the study is outlined, identifying and social background data are obtained, information about the sequence of events and decision antecedent to the marriage is obtained, and exploration of the current marital relationship is initiated.

2. Two separate interviews at NIH are carried out with each spouse to explore a) the history of developmental relationships with father and with mother (with regard to nurturance-availability, feeding, physical affection, and other areas of high satisfaction or conflict); b) current sexual adjustment and current marital conflict or satisfaction; and c) the prospective images of self and spouse as parents as well as of the fantasied first infant.

3. A final joint interview is then carried out in the home during which exploration of the current patterns of marital interaction is completed, any anxieties or questions stirred by our investigation are dealt with, and the conditions for possible future contact between the project and the couple are clarified.

B. Observations of Marital Interaction:

1. The color-matching test: This 15-minute experiment presents the couple with 20 swatches of color in standard sequence, with the instructions to come to an agreement between themselves as to which color best matches the experimenter's colors. Unbeknownst to the couple, the situation is arranged so that in 10 out of the 20 attempts to match colors with the experimenter no agreement is in fact possible. In these 10 instances the couple is faced, in effect, with a situation in which each perceives reality in a different way and in which there is no immediate clue as to the source of the conflicting perceptions. Their responses are tape recorded and analyzed to reflect the degree of difficulty in finding a resolution for each conflict and the modes of decision-making employed in response to this type of ambiguity stress. We believe it may be valuable to note here which couples remain psychologically aligned with each other against the confusing experimental situation and which couples are lured into a stubborn power struggle with each other. The maintainance or failure to maintain, psychological alignment under ambiguity stress may be predictive of subsequent coping behavior by the couple in new or strange situations.

2. The Improvisations: These are a series of four psychodramatic scenes, four to six minutes in length, in which the couple enacts a situation containing a conflict of goals (intentions). Here we record the verbal behavior and analyze for contrasting patterns of conflict resolution; we also observe certain non-verbal aspects of interpersonal behavior in the midst of conflict, particularly the employment of physical closeness or physical distancing maneuvers as part of the pattern of conflict resolution. The degree of empathy evidenced in communication and the degree of face-saving in decision-making are also of interest here.

C. Questionnaires:

1. The Daily Dilemmas: This questionnaire assesses the relative salience of seven areas of marital interaction within each spouse's conscious value system. The form of the instrument permits a ranking of relative salience for parental planning activity, feeding activities, housekeeping, physical affection, occupation, contacts with close relatives and contact with friends, by the method of paired comparisons. In preliminary data on 22 couples it appears that newlyweds may consider the activity areas of parental planning, feeding and physical contact to be highly salient as sources of satisfaction and that the area of occupation is of low salience as a source of satisfaction. Studies in the literature suggest that disparity in values between middle class husbands and wives may accompany conflicted marriage.

2. The Daily Routines Inventory: This instrument is modeled after the approaches of Herbst, Hoffmann, and others, and provides an opportunity for each spouse to describe current activities and decision-making patterns for self and for spouse (in the seven areas noted above) in terms of relative frequency of participation. A second form of the Daily Routines gets at the "ideal" image of the partners' participation in these seven action areas at a future time when they have had a newborn infant to care for.

3. Marital Empathy Inventory: This questionnaire presents 14 situations of conflicting wishes between a hypothetical husband and wife pair. It provides an opportunity for the subject to choose between four resolutions for each conflict: a resolution in which only the husband's position is recognized, a resolution in which only the wife's position is recognized, and two compromise (empathic, "role taking") types of resolution, one in which the wife's and another in which the husband's needs take moderate precedence. These measures of empathy in the marriage can be examined cross sectionally in relation to observational data obtained during the color matching experiment and the improvisations and also longitudinally in relation to aspects of non-verbal communication in the initial parent-infant relationship.

4. The Locke-Wallace Marital Adjustment Inventory, an instrument which has been used in a number of published studies, is being used as a global index of "marital adjustment."

5. In order to supplement our interview data with certain concrete informational items more economically gathered in questionnaire form, we have devised an Interview Supplement Questinnaire. The interview itself focuses somewhat more on affect-laden aspects of the marriage, such as satisfactions or values with regard to current activities; this supplemental questionnaire includes such information items as the frequency of visiting with relatives, or the frequency of shared versus segregated housekeeping activities, etc.

In order to clarify the relationship of the questions asked by the Study to the methods described above, we have prepared a series of charts to locate types of data. (see Appendices I - VII).

IV Data analysis:

From the foregoing it is apparent that the Couples Study, as now designed in the pilot phase of the work, is oriented toward a rather wide range of problems. Over the course of the next year we anticipate reducing our focus considerably--particularly as regards the general dimensions of the marital relationship. The choice of patterns to explore further, we feel at this stage of our knowledge, would be best based empirically upon pattern analyses of data gathered by a wide net, on the initial group of 40 couples. In this analysis of data we plan wherever possible to use direct coding of interview content and behavioral indices rather than to rely solely on ratings or interviewer judgments. With regard to the statistical processing of the data, we intend to rely on a combination of factor analytic and other correlation techniques, and appropriate nonparametric tests. During the course of this research we will obtain from each couple some similar data at several points in time, we will be able to assess patterns of change by use of panel analysis procedures.

FUTURE DIRECTIONS

The program outlined in this annual report can be characterized overall as exploratory research. Because we are looking in new ways at phenomena which have, for the most part, not been examined in these ways, there seems little doubt that, at a descriptive level, observations of salient new patterns of early family development will be obtained. Since the approach includes systematic assessment techniques as well, we are confident that defined relationships between certain variables will emerge, which may clarify the nature of the early developmental tasks of the family or the nature of certain family styles of coping with these tasks. These research results of the program, gratifying as they will be, should they be produced, will not satisfy; for a primary scientific need is for new and powerful concepts. Theoretical concepts are needed which will integrate the complex and diverse events and processes within the family structure in new ways, events and processes which, under varieties of contingent circumstances, can become relevant to the mastery or the failure to master a developmental task. (see footnotes 2 and 3).

The establishment of this developmental research unit has required two years so far, since its initial proposal; in some respects the operation is as yet in formative stages. One can legitimately inquire what opportunities for worthwhile extensions of the current program - using the current operations as a basic administrative structure - could be envisaged beyond 1963. Based upon the data of the 1961 pilot study, we now assume that several large samples of families can be usefully obtained, each sample being employed to test a different set of hypotheses, growing out of the pilot study. There also is the possibility that the data of the pilot study will indicate the need for a much heavier research investment in the study of pregnancy, as an intermediate phase between the newlywed and the neonatal phases, before very many valid conclusions can be drawn about developmental continuities from our data.

With the remodeling of several rooms in the building in the next year, it may be possible to vacate the apartment and make it available for the round-the-clock observation of infant behavior and of parent-infant interaction patterns in a way not previously possible. Sooner or later, too, it would seem worthwhile to relate these developmental studies directly to a study of emerging psychopathology or ego strength in the preschool child. Informal observations suggest the ready availability in currently observed samples of children of adequate numbers of cases of separation anxiety or of problems in impulse control (??pre-hyperaggressive children); it seems likely that some of our developmental variables have systematic relationship to the occurrence of such syndromes. Finally, it does not seem inconceivable that at some future date, a productive liaison may become possible with other laboratories at the National Institutes of Health, which are also interested in developmental problems, but from a more purely physiological point of view. This liaison would supplement our current collaborative arrangements with the Laboratory of Psychology and of Socio-Environmental Studies.

APPENDIX

I. SOCIO-ECONOMIC AND OTHER IDENTIFYING DATA
(Data gathered in the First Home Interview)

	Husband	Wife	His Parents	Her Parents
Birthplace				
Occupation				
Financial			This Data Not Obtained	This Data Not Obtained
Education				
Religion				
Siblings			This Data Not Obtained	This Data Not Obtained

II. MARITAL CAREER DATA
(Data gathered in the First Home Interview)

Events:

First meeting
Courtship
Decision to marry
Engagement
Wedding
Honeymoon
Initial plans for parenthood
Setting up housekeeping
First separation
Initial sexual adjustment
Initial adaptation to in-laws

APPENDIX

III. CURRENT MARITAL RELATIONSHIP: GENERAL ATTRIBUTES, NOT SPECIFIC TO AREA OF INTERACTION

Attributes	METHODS				
	Home (Joint) Interview	Individual Interview	Questionnaires	Improvisations	Color-Matching
Expression vs. inhibition of feelings	X	X		X	
Empathy - Insensitivity	X	X	X	X	
Influence: Dominance-Submission	X		X	X	X
Form of Decision-making in Conflict Situations		X		X	X
Overall "Adjustment"			X		
Free Predictive Hypotheses on Basis of Clinical Formulation	X	X			

X: Designates the methods used to assess each general attribute of the current marital relationship.

APPENDIX

IV. CURRENT MARITAL RELATIONSHIP:

ATTRIBUTES SPECIFIC TO AREAS OF INTERACTION

(Assessed in the Joint Home Interview)

	AREA OF INTERACTION								
	Feeding-Eating	Sexual	Involving Close Relatives	Parental Planning	Occupation of Husband	Occupation of Wife	Housekeeping	Friends	Other: Religion, Avocation, Education, Budget, Etc.
1. Participation in the area tends to be shared or segregated	X		X	X			X	X	X
2. Decision-making in the area tends to be an easy collaboration or marked by difficult resolutions	X		X	X	X	X	X	X	X

X: Designates the methods used to assess each general attribute of the current marital relationship.

APPENDIX

V. ATTRIBUTES OF EACH SPOUSE'S ATTITUDES OR BEHAVIOR, IN RELATION TO THE PARTNER, IN SPECIFIC SITUATIONS:

Assessed in Various Ways: H = Home Interview
I = Individual Interview
(I) = Optionally in Individual Interview
Q = Questionnaire

(In boxes left blank, no assessment is made)

Attributes	Feeding-Eating	Sexual	Involving Close Relatives	Parental Planning	Occupation of Husband	Occupation of Wife	Housekeeping	Friends	Other: Religion, Avocation, Education, Budget, Etc.
1. Area is clearly important (salient) or clearly indifferent (not salient)	H Q	I	H Q	I H Q	H	H Q	H Q	Q	
2. Tends to be clearly more influential or clearly less influential in decisions in the area	H Q	I	H Q	H Q	H	H Q	H Q	H Q	
3. Tends to have clear satisfaction or dissatisfaction (frustration) with spouse's attitude or activity in the area	H (I)	I	I	H I	H (I)		H (I)	H (I)	
4. Tends to have clear self-satisfaction or conflict about self in the area	H (I)	I	I			H (I)	H (I)		
5. Tends to take a nurturant supportive attitude toward the spouse in the area, or to neglect and ignore him	H	I					H		
6. Tends to demand help or support from spouse in the area, or to accuse and complain about spouse	H	I					H		
7. Frequency of participation	Q	Q	Q	Q	Q	Q	Q	Q	
8. Empathy-insensitivity in conflict decisions	Q		Q	Q	Q	Q	Q	Q	

APPENDIX

VI. IMAGE OF DEVELOPMENTAL RELATIONSHIPS WITH PARENTS

(Data gathered in the Individual Interview)

Area		Mother	Father
1. Food	a. Eating and family socialization b. Affective experience around food, itself		
2. Affectional Physical Contact	a. Individual experiences b. Family as a unit		
3. Nurturance-Neglect	a. Self-attitude in relation to family b. Parental attitudes		
4. Impulsivity-Control	a. Family pattern b. Individual pattern c. School performance		

APPENDIX

VII. PROSPECTIVE FANTASIES ABOUT PARENT-INFANT RELATIONSHIPS
(Assessed in Individual Interview)

A.

	Self Infant	Spouse Infant
Feeding		N.O.
Physical Contact		N.O.
General Nurturance		N.O.
Other: Nonspecific, exploratory		

B.

	Subject's Actual Experience with Infants in Past
Feeding	
Physical Contact	
General Nurturance	
Other	

C.

	Self
Possible Marital Role Changes with Arrival of Infant	
Possible Occupational Role Changes with Arrival of Infant	
Other Changes with Arrival of Infant	

N.O.: Data not obtained in current design.

Clinical Neuropharmacology Research Center
NIMH-Saint Elizabeths Hospital
J. Elkes, Chief

The past year has seen a further development of the collaborative program between CNRC and Saint Elizabeths Hospital, and given strong indication of the viability and potential of the symbiotic arrangement entered into by C.I., NIMH, and Saint Elizabeths Hospital. The Hospital has established eleven research positions for the development of research within the Hospital; these are being filled in consultation with the CNRC to complement the activities of the CNRC. Dr. F. N. Waldrop, Associate Director of Research for Saint Elizabeths Hospital (a Saint Elizabeth staff member) has done much to coordinate research activities, both within and outside the William A. White Service, and to further collaborative studies between Saint Elizabeths Hospital and CNRC staff. The Research Committee of the Hospital (composed of Senior staff members of the Hospital, and of the CNRC) has continued to provide a useful planning board for the development of research throughout the Hospital, and has served as a channel of communication between the NIMH and the Hospital. A small Senior Staff Committee has recently been appointed to consider matters of planning and policy within the Hospital, and make appropriate recommendations to the Superintendent. Both the Chief, CNRC (as Director of Research of the Hospital) and the Associate Director of Research of the Hospital (Dr. F. N. Waldrop) serve on this Committee. Among matters now being discussed by this body are the changing patterns of treatment throughout the Hospital, and the evolution of new Clinical Care Facilities (such as Day and Night Hospital, and possible O.P. Clinics) geared to the needs of the Community of which the Hospital is a part. A Program Consultation Committee has been created within the Hospital to advise the various Services in bringing about changes in their Therapeutic Programs. The Laboratory of Socio-Environmental Studies of CI, NIMH, as well as the CNRC, have been invited to participate in these various operations; and, thus, are likely to benefit from an unusual opportunity for studying a long standing and leading institution during a period of active change and evolution. Equally, the Pathological Laboratory Services of the Hospital have been recently strengthened by the provision of new equipment, and the Laboratory is now able to partake in research activities more actively than hitherto. The Personnel and Engineering Branch of the Hospital have been helpful to the CNRC on many occasions. Throughout all these phases, the Superintendent of the Hospital, Dr. Winfred Overholser, and the Assistant Superintendent, Dr. Dale Cameron, have shown the CNRC and its individual members every consideration, courtesy, and support. The fact that a number of CNRC staff live on the Hospital grounds is a fitting illustration of the many human links which have developed between the CNRC and the Hospital, and which are closing the respective segments of the joint operating into a comprehensive and representative whole.

Dr. Irwin Feinberg, who joined the Center in July, 1960, from the Laboratory of Clinical Science is spending the present academic year in the laboratory of Dr. Jean Piaget, in Geneva, Switzerland. Similarly, the laboratories of the CNRC have accommodated three Guest Workers, during the past year: Dr. Leiv Gjessing of the Dikemark Municipal Hospital, Oslo, Norway, working with Dr. H. Weil-Malherbe; Dr. R. von Baumgarten, Professor of Physiology, University of Göttingen, Göttingen, Germany, working with Dr. G.C. Salmoiraghi; and Dr. R. Whalen, Research Fellow, from the Department of Psychology, University of California, Berkeley, California.

The CNRC has been visited by some one hundred and eighty visitors during the past year. Twenty Guest Seminars have been held, some of them planned jointly with the Hospital.

Section on Psychiatry

As hitherto, the clinical studies of CNRC have centered on problems of the care and the treatment (including pharmacotherapy) of the chronic schizophrenic patient. This aspect was chosen for three separate reasons. In the first place, the chronic schizophrenic patient forms the numerically preponderant problem of the Hospital, and it was hoped that any examination of this problem could be of service to the Hospital. Secondly, the relative stability of a chronic population offers an opportunity for the calibration of research methods and instruments which are likely, at a later stage, to find their application in the more mobile populations of an acute admission service. Lastly, the establishment of a sound clinical care program within the William A. White Service was judged a necessary preliminary to the pursuit of a more discrete program of clinical investigation of selected conditions and syndromes, including metabolic studies in man.

As mentioned in the last year's report, a comparative drug study involving two tranquillizers and a placebo was initiated by Dr. A. Hordern, Visiting Scientist, and Dr. J. Lofft, of the Saint Elizabeths Hospital staff. This study was planned to proceed simultaneously on six wards of the William A. White Service of Saint Elizabeths Hospital. As well as being a drug study, the investigation was intended to examine in some detail, and with special emphasis on sources of error, the effects of non-drug factors known to profoundly affect the response to medication in a typical mental hospital setting. Essentially, the study thus aimed at (1) determining the effect of physical environment on the responsiveness to drugs; (2) determining the effect of various types of nursing care and, particularly, nursing in small groups, on drug response; (3) the cultivation of native therapeutic and research skills often found, but ignored, in ward personnel; (4) the codification of a number of questions commonly entered into a drug trial in a mental hospital

setting, (i.e., the Selection of Patients, Selection of Drugs, Selection of Experimental Design, the Technique of Drug Administration in a Blind Study, the Assessment of Side Effects, Management of Adequate Laboratory Control, and the Comparison of a number of Clinical Evaluative Techniques); (5) the monitoring of attitudes toward research; and (6) the institution of data reduction techniques suited to a drug study conducted in this manner. The dimension of the study was kept within the limits of applicability and feasibility in a mental hospital setting so as to encourage a re-testing of the conclusions in other Services of Saint Elizabeths Hospital and, conceivably, other state institutions. An analysis of the data, carried out by Dr. Wilson Taylor, though not yet complete, has pointed to several powerful sources of error. Some positive and empirical trends, however, are equally apparent. A coordinated program of clinical investigation proceeding simultaneously in a number of wards of a mental hospital building (rather than a single "research service") can profoundly, and with great economy, contribute to the raising of both therapeutic and research skills of personnel throughout such a building. The systematic review of methods and of data can become an instrument of education of personnel. Nursing in small groups, structured around the skills of attendants and of well preserved patients, can act as a pacemaker in profoundly changing the therapeutic climate of a chronic ward. Such a program, while contributing to the rehabilitation of patients, reduces the consumption of tranquillizers on a ward; it also changes attitudes of personnel. Rating scales, while having their uses, also have their serious limitations. Some documents furnish much higher inter-rater reliability than others, and some are more sensitive to fluctuations in the clinical picture over time than others.

The above study was replicated by Dr. M. Hamilton (Visiting Scientist) and Dr. F. N. Waldrop, in 63 male and 63 female patients selected for the degree of their chronicity and the severity of their symptoms, and transferred to the William A. White Service for the purpose. Prochlorperazine, Trifluoperazine, and inert placebo were compared, in a 3-way factorial design, with the effects of intensive nursing and social manipulative procedures; the design allowing for an evaluation of the effectiveness of drugs, and social therapy independently and in conjunction. Both drugs were found effective in the doses given, the effect being achieved in from three to five weeks. Social and group nursing techniques alone (i.e., in the absence of drugs) led to a significant reduction in symptoms on the male wards, but not on the female wards; the effects (in the male wards) being comparable to those achieved by drugs alone. On the female ward, the moderate improvement due to chlorproperazine could be enhanced by group nursing techniques. This study, like its predecessor, pointed to many pitfalls in any investigation in chronic schizophrenic patients which attempts to make

due allowance for non-drug factors entering into a treatment program. It may be noted that cognate research designs are now being used in other parts of Saint Elizabeths Hospital, and that, at the initiative of the Hospital staff, Group Nursing Techniques as used in William A. White Service are now being tested in other wards. The Research Nurse, Mrs. Helen Sainato, has been invited to present a paper on the work at the coming meeting of the American Psychiatric Association. With the cooperation of the Medical Arts Section of the Division of Research Services, NIH, the initial methodological study has been made the subject of a Teaching and Demonstration Exhibit. This was shown at the 116th Annual Meeting of the American Psychiatric Association in Atlantic City in May, 1960, and the 14th Clinical Meeting of the American Medical Association. Requests for the documents used in this study have been received from over 100 State institutions.

In the context of the above study, and also as a part of an independent program in Social Rehabilitation on his ward, Dr. Sheppard Kellam has now had one year's experience in the use of his Social Contact Matrix for measuring, in an objective manner, the amount and pattern of social contact of a patient in a ward setting. The instrument has been found useful and sensitive in quantifying changes brought about by psychoactive drugs, and group nursing techniques. Dr. Kellam is now attempting a correlation between Symptom Fluctuations in the individual patient and the pattern of social contact by the patient. He is also collaborating in the multi-hospital drug study organized by the Psychopharmacology Service Center, and will thus have a further opportunity to use the Matrix in a setting other than Saint Elizabeths Hospital.

A number of joint studies between the CNRC and other laboratories of CI, NIMH, are also proceeding. Dr. Irwin Feinberg, in conjunction with Dr. Roger McDonald of the Laboratory of Clinical Science, has examined the excretion of vanyllyl mandelic acid (VMA) in patients suffering from depression and treated with electro convulsive therapy. Data from only eight subjects are available to date. Some very high levels of VMA excretion before any treatment have been noted in these patients, suggesting, possibly, that such patients may be producing epinephrine in abnormally large quantities. Age as a variable, however, has not been allowed for in these subjects, and an extension of the series is needed before any conclusion can be drawn. In conjunction with Dr. Carlson, of the Laboratory of Psychology, Dr. Feinberg and Mr. R. Koresko have also examined the ability of schizophrenics to perceive velocity (i.e. predict the time of arrival of a moving line at a target point after its disappearance). This response has been studied in some 40 patients. It was found that many schizophrenics, while responding appropriately to varying speeds and

target distances, still manifest a markedly prolonged delay. The evidence so far does not suggest that this delay may be necessarily related to a lengthening of the reaction time (a function notoriously disturbed in schizophrenia). In yet a third study, Dr. Feinberg has examined (in conjunction with Dr. Frederick Snyder, of the Adult Psychiatry Branch, and Mr. Richard Koresko), the quantity of dreaming in non-hallucinating and hallucinating schizophrenics. The technique of Kleitman and Dement (in which EEG and eye movements are used to monitor and signal dream activity) was used. The results so far suggest that the amount of dreaming does not differ significantly in the two groups. This study was carried out in patients hospitalized for brief studies only. It will be extended to more chronic patients during the coming year after Dr. Feinberg's return from Dr. Piaget's Laboratory.

In sum, then, the clinical activities of the Clinical Neuropharmacology Research Center during the past year have been expended in creating within the William A. White Service a standard of care and observation which will serve as a necessary prerequisite for the more detailed studies which are now being planned. It is also hoped that the medico-legal problems connected with the prosecution of investigative work within the William A. White Service will have been resolved in the foreseeable future; Dr. Winfred Overholser is giving these endeavors his personal support.

Section of Chemical Pharmacology

In pursuit of an old standing interest, Dr. H. Weil-Malherbe, together with Dr. E. R. B. Smith, has continued with studies aiming at developing reliable, sensitive, and specific methods for the routine assay of catecholamines in plasma. By combining an ion exchange procedure with chromatography on alumina, an additional purification of plasma extracts could be obtained without sacrifice in accuracy or sensitivity. In Dr. Weil-Malherbe's hands the ethylenediamine method has yielded results in good agreement with those obtained by the trihydroxyindole method. The ethylenediamine method, however, resulted in a fourfold increase in sensitivity, thus potentially allowing the measurement of concentrations of 0.1 micrograms of catecholamines per liter. Similarly, Dr. H. Weil-Malherbe and Dr. E. R. B. Smith have developed methods for the differential estimation of metanephrine and normetanephrine, 3-4 dihydroxyphenylacetic and 3-4 dihydroxymandelic acid in urine. These methods will be put to use in material obtained from subjects in various stress situations. The NASA Space Task Group have invited collaboration in these studies. In a cognate area, Dr. H. Weil-Malherbe together with Dr. Axelrod and G. Hertting (of the Section of Pharmacology, Laboratory of Clinical Science) are studying the penetration of tritium labelled epinephrine and norepinephrine into various parts of the brain, and into the pituitary gland. Previous studies had shown that the amounts of radioactive epinephrine and norepinephrine penetrating into most

parts of the brain are very small, and could probably be accounted for by the blood content of the tissue. In the hypothalamus, however, larger amounts were consistently found; though even in this area the uptake appeared slower than in most extracerebral tissues. It was shown that a number of drugs, (including chlorpromazine, cocaine, and tyramine) which block the uptake of norepinephrine by extracerebral tissue, (particularly heart) do not affect the accumulation of radioactive norepinephrine in the hypothalamus. The relative freedom of entry into the hypothalamus seems to be specific for norepinephrine and epinephrine. It was also found that the pituitary gland takes up circulating norepinephrine rapidly and with great activity. The results suggest that the so-called central effects of epinephrine may in part be mediated by the sensitivity of the hypothalamus to this agent.

Dr. Weil-Malherbe and Dr. H. Posner have also pursued further their studies on the effects of various drugs on the concentrations, and in the intracellular distribution, of catecholamines within the brain. Previous studies (by Dr. Weil-Malherbe and his colleagues) had shown that brain catecholamines may be separated into two intracellular franctions, one present in the cytoplasmic sap and the other sequestered in particulate matter. According to current concepts only the former is biologically active while the latter may serve as store. The effect of reserpine, phenylisopropylhydrazine (Catron, a monoamine oxidase inhibitor), pyrogallol, (an inhibitor of the enzyme catechol-O-methyl transferase), and 3:4-dihydroxyphenylalanine (DOPA) alone and in combination have been examined. In keeping with previous observations may be Dr. Weil-Malherbe, reserpine was found to cause a more rapid depletion of the soluble than the particulate fraction. This action was inhibited by phenylisopropylhydrazine (Catron), but not by pyrogallol. Phenylisopropylhydrazine alone induced a rise in norepinephrine concentration in the soluble fraction only, without significantly affecting the concentration of dopamine. Pyrogallol alone had no significant effect but was found to potentiate the action of phenylisopropylhydrazine, as well as of dopa, suggesting, for the first time, the involvement of the enzyme catechol-O-methyl transferase in the endogenous metabolism of brain catecholamines. These findings compel a re-evaluation of the suggested role of reserpine in terms of storage and release of catecholamines within the brain, and focus attention on the importance of intracellular economy and metabolic compartmentilization in the mode of action of the phrenotropic drugs.

In pursuit of previous studies, Dr. H. Posner has continued to examine the intermediate metabolism of chlorpromazine and related compounds in the human body. He has shown the existence of at least four different phenolic metabolites of chlorpromazine and promazine which are excreted in the urine as conjugates of glucuronic acid. The chlorpromazine sulfoxide would appear to be a minor metabolite of chlorpromazine. Owing to a lack of reference substances of known constitution, it has so far not been possible definitely to identify

any of the metabolites. It is hoped, however, that as the substances become available the possible relationship between pharmacological activity of chlorpromazine and of its metabolic products may be further clarified. Such studies are being planned in conjunction with Dr. Cosmides of the Staff of the Psychopharmacology Service Center. In a cognate vein Dr. Posner, together with Dr. J. D. Solomon (Director, Pathological Laboratories, of Saint Elizabeths Hospital) have examined the tests now available for the identification of phenothiazines in the urine and with special reference to the validity of the Forrest and Forrest Reaction. It was shown that whereas the test was reliable for chlorpromazine, it was apt to give false positive reaction for piperazine linked phenothiazines. Since the test is being used in the control of phenothiazine medication, a re-examination of it is in place.

Dr. Szara together with Miss F. Putney has continued to study the intermediate metabolism of psychotropic tryptamine derivatives with special reference to dimethytryptamine and N.N. diethyltryptamine. More recently he has added a third psychosomimetic indole derivative, -methyltryptamine to the compounds already examined. The side chain of the -methyltryptamine is identical with that of amphetamine, and it was found to undergo deamination similar to amphetamine. A scheme for the metabolism of -methyltryptamine has been proposed; this, once again, has stressed the importance of 6-hydroxylation in the metabolic handling of the drug. Dr. Szara has also improved his method for determining the 6-hydroxydiethyltryptamine in urine. This is now suitable for measuring small amounts of the substance in metabolic experiments in man.

These biochemical studies have been linked to behavioral observations, both in the experimental animal and in man. The animal studies (carried out in conjunction with Dr. Eliot Hearst) aimed at establishing the effects of psychotomimetic tryptamine derivatives, and their metabolites, on several types of behavior in various species and to correlate behavioral effects with metabolic variables in the same subject; an attempt is also being made to correlate behavioral effects with chemical structure and the chemical properties of various tryptamine derivatives. The early findings in rats (reported previously)have been confirmed and extended to both monkeys and pigeons. It was shown that the doses required to elicit a significant effect on performance (both in reward and avoidance situations) was lower for 6-hydroxydiethyltryptamine (the major metabolite of diethyltryptamine) than that for the parent substance (diethyltryptamine). Substances closely related in chemical structure to diethyltryptamine which are 6-hydroxylated (for example, -methyltryptamine) were found to have behavioral effects in rats and monkeys, whereas other structurally related substances (such as dihexyltryptamine) which are not hydroxylated exerted no behavioral effects. -methyltryptamine, which has a slower rate of hydroxylation than diethyltryptamine, also exerts a more prolonged behavioral effect than diethyltryptamine.

It will be particularly interesting also to examine a number of inhibitors of 6-hydroxylation. Dihexyltryptamine inhibits the reaction competitively.

The effects in man of NN-diethyltryptamine are being examined in conjunction with several members of the Laboratories of Clinical Science and of Psychology, CI, in the multidisciplinary research ward at the Clinical Center. The project is intended to provide information on the relationship between the intensity of psychological effects of NN-diethyltryptamine and the metabolism (and especially the rate of 6-hydroxylation) of the drug. The drug is being given to chronic schizophrenic patients, and will be given to a number of acute schizophrenic patients and to normal volunteers. Since the study is in progress, no report can be made at the present time.

Section on Behavioral Science

Following a study initiated last year, Dr. Eliot Hearst has continued to examine the generalization gradients for reward and punishment-controlled behavior in the Rhesus monkey. Baseline data in this area are lacking and are much needed for the appraisal of the effect of drugs on these functions in various motivational situations. It was assumed that the extent to which a subject may respond to a stimulus which resembles (but does not exactly correspond to) a stimulus used in an original conditioning situation may be a function of the type of motivation controlling the behavior at the time of the experiment. Dr. Hearst has used Intensity of Lighting (accompanying either reward or punishment behavior) as the conditioning stimulus, and measured generalization gradients between various intensities in conditions of reward and punishment. He has shown that generalization gradients for punishment controlled behavior were apt to be much flatter than for reward controlled behavior; there being much more stimulus generalization under aversive conditions than under reward conditions. It was also shown that after discrimination training (i.e. the animals being specifically trained to respond to a bright light and not to respond to a dim light, and vice versa), both gradients were much steeper, but, nevertheless, avoidance gradients still were flatter than reward gradients. These studies are now being extended to auditory conditioning experiments and form a necessary preliminary to the study of effects of drugs and, quite possibly, of surgical lesions, or generalization. Since it has been suggested that the amygdala may have a specific function with regard to stimulus generalization, lesions in this area will be of particular interest.

Dr. Eliot Hearst has also examined the "resistance to extinction" function in pigeons, and is investigating the delayed alternating responding in pigeons, with special reference

to the action of hyoscine, amphetamine, and barbiturates. Since this function shows some impairment in monkeys following lesions to the frontal lobe, and has also been shown to be affected by LSD-25, a study of this type of response in birds seemed worthy of examination.

In pursuit of studies carried on with the Department of Psychology at Berkeley, University of California, and also studies initiated at CNRC by Dr. R. P. Michael, Dr. Richard Whalen has embarked on a detailed examination of the environmental and physiological factors entering into sexual behavior in the cat. The pattern was chosen as a relatively stable pattern of behavior, and the physiological studies are designed to delimit the areas in the Central Nervous System respectively concerned with sexual arousal, ejaculation, and the effects of prolonged mating. It is hoped to develop a method for the local application of drugs to selected areas of the hypothalamus, and to record from relevant areas in the brain stem during mating. The studies should be of interest in view of the studies pursued in the Section of Limbic Integration in the Laboratory of Neurophysiology, NIMH.

Electrophysiological studies have centered on an examination of direct current (D.C.) changes in the cortex of the cat, an analysis of evoked potentials in the cortex and the geniculate body of the cat, and an examination of the patterns of discharge of respiratory and cardiovascular neurones in the cat, and in fish. Dr. Robert Gumnit, using a compact, sensitive, stable nonpolarizable electrode of his own design, has developed a method for recording Direct Current potential changes in the lightly anesthetized, and the conscious animal. The effect of auditory stimulation on these responses has been examined, and the localization of the changes in various areas of the cortex has also been studied. The method represents a definite technical advance in the recording of D.C. changes on the surface of the brain. The role of these slow shifts and their relation to the handling of sensory information by the brain is a matter of great interest, and, indeed controversy. The demonstration of the existence of these D.C. changes will provide a basis for further pharmacological enquiry. Of particular interest is the demonstration of D.C. potential changes (previously observed only in anesthetized animals) in the conscious, unanesthetized animal; and the response of these changes to auditory stimulation. These studies were carried out in conjunction with Dr. R. G. Grossman of the Walter Reed Army Institute for Research.

The subject of evoked potentials has also been pursued by Dr. Arthur S. Schwartz, who is studying the effects of small doses of LSD-25 on visual and auditory evoked potentials, with special reference to differences in response in these two pathways. These studies represent an extension of the work done by Dr. E. V. Evarts,of the Laboratory of Clinical Science. Dr. Schwarts is also examining the role of the visual cortex in flicker discrimination and critical flicker frequence in the cat.

Dr. G. C. Salmoiraghi has pursued his independent investigation of the localization and patterns of discharge of the respiratory and cardiovascular neurones in the brain stem of the cat. In conjunction with Dr. Rudolf von Baumgarten, Professor of Physiology, University of Göttingen, Göttingen, Germany, who visited Dr. Salmoiraghi's laboratory for some six weeks during the summer, intra-cellular potentials from respiratory neurones in the brain stem of the cat were obtained. These represent the first intracellular recording from neurones in the lower brain stem. The data have amplified and extended the previously published data on the nature of rhythmic discharge of neurones in the so-called respiratory areas. They have suggested that three factors may contribute to produce rhythmic discharge of respiratory neurones; namely, a self-reexciting mechanism within the inspiratory and expiratory networks of the neurones tending to maintain activity within these networks; some self-limiting mechanisms tending to limit the frequency and duration of the discharge; and an arrangement of reciprocal innervation which provides inhibition of one network when the other one is active. The findings have also suggested that the increase in the firing threshold, as a burst of action potentials progresses, may play a major part in regularly bringing the discharge to an end. A similar program has been followed in localizing the patterns of discharge of respiratory neurones in the goldfish. Respiratory potentials could be recorded from two relatively narrow strips, one on each side of the brain stem. These potentials could be divided into two groups depending on whether they occurred concurrently with the abduction or adduction of the gill covers. Neurones of either group, however, were found to behave rhythmically even after abolition of all respiratory movement by succinylcholine. The evidence suggested that the rhythmicity of discharge in the goldfish depends on mechanism or mechanisms not unlike those operating in the mammalian nervous system.

In a cognate vein, Dr. Salmoiraghi is now proceeding to localize the patterns of electrical discharge of cells related to the central control of blood pressure, and to analyze the mechanisms affecting repetitive discharge in these neurones. These physiological data will be used in subsequent analysis of the effects of drugs upon the central steering mechanisms governing respiration and blood pressure. If technically possible, drugs will be applied locally by multibarelled micropipette to cells in the relevant areas of the brain stem.

A welcome feature throughout the past year has been the marked interaction between the activities of the various sections. It is to be hoped that with the emergence of a stable organization, and the clear definition of some central themes to which the Center wishes to be committed, this interaction will increase, leading, in time, to a yield greater than the sum of individual endeavors.

Laboratory of Psychology
David Shakow, Chief

The primary areas of research carried on in the combined Laboratory have remained essentially the same this year, though the experimental work has shown the natural development. The Section on Animal Behavior has continued its attempt to define the behavior served by association cortex in man, chimpanzee, and monkey, and to define the neural mechanisms underlying this behavior. In addition, considerable effort has been expended in attempting to specify the neural mechanisms underlying motivation and attention in monkeys and man. The section on Learning and Perception has, on the one hand, continued its studies of the effects of the physical structure of the environment on instinctive and social behavior in rats and on the other its studies of the nature of the perceptual process as reflected in size-constancy and in velocity. The Section on Aging has expanded its previous studies of the behavioral and physiological changes associated with age, concentrating especially upon the age-related impairment of higher cognitive processes. The Section on Child Development has advanced in its attack on problems of behavioral development, particularly during the first year of life, using statistical analytic techniques on longitudinal data, normative and experimental studies. The Section on Personality has become heavily involved in a series of experimental studies on processes affecting cognitive restructuring which were only in the planning stage last year. The Section has, however, continued its studies on the non-contentual components of speech as related to the communication process, and on psychosomatic studies related to stress. In the Office of the Chief the majro concern has been with two areas: (1) psychology of schizophrenia -- the problems of preparatory set, cognitive and perceptual processes, and the relative influence of environmental psychological and hereditary factors; and (2) the psychotherapeutic process -- the microscopic aspects of the communication of affect in therapy, and the limits of psychotherapy for realizing potentialities.

The relevant aspects of the reports of the several Section Chiefs follow.

Section on Child Development

The concern of the Section on Child Development is to increase understanding of the processes of behavioral development, primarily during the first years of life. The emphasis is on the normal processes as necessary bases both for promoting healthy growth and for evaluating and diagnosing the pathological. Its work is based on the hypothesis that genetic determiners of behavior become manifest during the processes of maturation, and

that the maturation of the organism occurs only as it interacts with relevant aspects of an environment which is in varying degrees favorable to the infant's growth and development.

Certain studies are designed to observe and describe, under standard conditions, the central tendencies and normal variations in mental, motor, emotional, and motivational development of infants in the first two years of life. In this program Dr. Bayley is revising, restandardizing, and extending her infant scales of mental and motor development. In doing this she has worked with the Collaborative Project of NINDB, as a consultant and by training their psychologists in testing procedures, in return for which they have furnished tests on 1200 infants aged 1-15 months. On the basis of these data, with the addition of about 300 tests given locally, preliminary revision of forms of the mental and motor scales have now been set up and are being used on a trial basis. The Infant Behavior Profile for evaluating normal development aspects of attitudinal and emotional behavior is still in the state of preliminary analysis. Further testing and statistical procedures for use in scoring the tests are currently under way as well as item analyses that may permit early diagnosis of central nervous system damage and other forms of retardation. The impetus for undertaking this program was the great need for an adequately standardized set of tests of infant development. The current battery was designed to include a broad band of relevant behaviors, to be standardized on a geographically and ethnically wide selection of infants, to bring the normative data for standardization up to date with current tests, and to clarify and improve the directions for observing, recording, and interpreting infant behaviors in response to standard materials and conditions, in the light of present psychological theory and knowledge. The many requests already received for the tests indicate the need for such instruments by physicians and psychologists who are making diagnoses and carrying out research programs with infants.

Another aspect of the standardization of the infant scales is the preparation of a motion picture which will demonstrate, for training purposes, testing procedures and characteristic responses of infants at successive ages. Pictures of the testing situations have been made, and are now in the process of being edited.

The program of development of the mental scales leads naturally into plans for more detailed studies of the mental processes involved. Thus, within the broader framework of standardizing the tests for evaluating general behavior development of infants, the Section hopes to institute a program to explore in more detail the early processes of perception, concept formation, and the general area of cognitive functioning in the first two years of life.

Dr. Rheingold's program of research is another approach to the study of normal developmental processes of infants. Her purpose is to investigate the process by which the human infant's response to social and non-social objects is modified by the responses these objects give to his exploratory activities. Classifying this behavior as a homeostatic drive, (the forerunner of behaviors labeled as sociability, curiosity, manipulatory drive, and play) she hypothesizes that at first the infant's responses to people and to things are similar and that differentiation of response occurs by a process of learning based on the different nature of the responses given to the infant's own overtures. At present she is studying the dimensions of novelty and complexity of stimuli, both spatial and temporal. The dimension of familiarity will also be explored. Maternal care is, of course, and important part of this program, as it is a major source of environmental stimulation for the infant, and operates both as evoking and reinforcing stimuli. Another part of this general program is a comparative study of social and exploratory behavior in other young mammals, together with their maternal care.

In this program Dr. Rheingold has employed three methods, depending upon the stage of the problem and the nature of the questions being asked. The first is the naturalistic observation of sequences of interaction between mother and child in their usual environments (in her study of measurement of maternal care). In the second method these naturally-occurring sequences of behavior are reproduced under controlled conditions, but still in the infant's usual environment (for example, the study of social conditioning of vocalizations in the human infant). The third method, which is now being perfected, seeks to control the presentation of the stimuli which result from the infant's own behavior, and to record the infant's response. This method of recording sequences of behavior with precision requires laboratory space and instrumentation which at present are inadequate. This experimental method is a very important step in making the detailed analyses of the processes observed in the naturalistic situations.

So far in these studies, observation has revealed that a considerable amount of time and energy is spent by the young infant in seeking a response from his environment, more from certain objects than from others. Measures of the responses to people and to things of three-month-old infants receiving different amounts of environmental stimulation (home and institution) revealed few differences. What differences did appear showed that infants receiving less day by day stimulation responded more quickly and more fully. Some non-social objects were effective in producing the smiles and vocalizations usually associated with responses to social objects, suggesting that the origins of the smiling response may be based on the stimulus properties of the object itself and not on the history of need-

reduction (e.g., maternal care). Pilot studies with three- and four-month-old infants indicate that panel-pressing may function as a free operant and that illumination of these panels when made contingent upon the infant's press may function as a reinforcer. In Dr. Rheingold's continuation of comparative studies of maternal care in mammals, the data on detailed observations of dogs is now being analyzed, but has not yet reached a state in which results can be reported.

A related area of research in which Dr. Schaefer has been active, in collaboration with Dr. Bayley, has been the exploration of maternal behavior, child behavior, and their interrelations in available data from her Berkeley Growth Study. Several articles have already been published from these studies, and two monographs are now in preparation. The first of these monographs, Maternal Behavior, Child Behavior, and their Interrelationships from Infancy through Adolescence, is almost ready for publication. Because of the currently strong interest in and the various theories about the effects of maternal care on the child's adjustment and personality development, these long-term records on a group of ch children who started life as healthy newborns, should yield important relevant information.

Data on the social and emotional development of 54 subjects had been systematically collected at frequent intervals from their birth in 1928 until they were 18 years of age by Nancy Bayley at the Institute of Human Development, University of California, Berkely, California. Observations of maternal behavior during infancy, interviews with the mothers at preadolescence, and the data on child behavior were organized and the interrelationships of the variables were computed at NIMH. A few of the many findings on consistency of both maternal behavior and child behavior through time, and on the relation of maternal behavior to child behavior are summarized below.

Maternal behavior from infancy to preadolescence is relatively consistent for a dimension of acceptance versus rejection but is relatively inconsistent for a dimension of autonomy versus control. Child behavior from infancy to adolescence is rather consistent for a dimension of extraversion versus introversion but is relatively inconsistent for a dimension of adjustment versus maladjustment. Maternal behavior is more highly related to child adjustment than is socioeconomic status, although maternal behavior is related to socioeconomic status, financial stress, and poor physical health. Maternal acceptance versus rejection is more highly related to child adjustment than is maternal granting autonomy versus control, suggesting that the controversy about permissiveness may be emphasizing a less important aspect of parental behavior. Maternal behavior during infancy is more highly related to sons' positive task-oriented

behavior at preadolescence than it is to the sons' behavior at three years, suggesting there may be a cumulative effect of maternal behavior upon sons' behavior. Maternal behavior during infancy is more highly related to sons' behavior at 9 to 12 years than is the sons' own behavior during infancy, suggesting that early maternal behavior may be more predictive of the child's future adjustment than is the child's own early behavior. For this sample boys' behavior is more highly related to earlier mothers' behavior than is girls' behavior although girls' behavior does relate to current maternal behavior. These results suggest that girls may respond more to their current interpersonal situation while boys may reflect their past relationships more. Additional data on the relationship of maternal behavior and the social and emotional behavior of the child to intellectual development are currently being analyzed.

Dr. Schaefer's interest in maternal behavior, methods of observing and recording it, its organization into a conceptual model, and its relation to child behavior, has led him into a series of related studies. He has checked his work on the Berkeley Growth Study material by successfully applying the methods to the tables of intercorrelations of maternal and child behavior variables derived from the studies of other investigators. He has worked on further development of methods for the study of maternal personality and behavior variables, in cooperation with the NINDB Collaborative Project. For this project he has developed two objective inventories, a Pregnancy Research Inventory and a Postnatal Research Inventory, for assessing the perinatal adjustment of mothers. Both inventories investigate psychosomatic symptoms of the mother and her psychological response to her current situation. These inventories were given to pregnant women and women soon after the birth of their child, and for a small sample the same women were given both inventories. The inventories were found to measure reliably several patterns of response. For the Pregnancy Inventory these are: 1. Dependency, Fears for Baby, and Fears for Self; 2. Depression, Irritability, and Lack of Desire for Pregnancy; and 3. Numerous psychosomatic symptoms before and during pregnancy, at menstruation, and at times of emotional stress. For the Postnatal Inventory, they are: 1. Fear or Concern for the Baby, Need for Reassurance, and Intrapunitiveness; 2. Negative Perception of Aspects of Child Rearing, Irritability, Depression, and Extrapunitiveness; and 3. Psychosomatic symptoms. There was evidence of consistency of characteristic patterns between the Pregnancy and Postnatal Inventories. The inventories have now been turned over to the NINDB Collaborative Project for actual use.

Dr. Schaefer has used yet another approach to measuring parent behavior by developing an inventory to administer to school children, on their perceptions of their parents' behavior, both mothers and fathers. He was able to develop a reliable

instrument which revealed two major dimensions -- love versus hostility, and autonomy versus control. Thus these replicate the conceptual structure of the model of maternal behavior previously obtained from observations of mothers' behavior. The children tended to describe both parents as behaving toward them in a very similar way, i.e., both hostile, or both loving, etc. In an exploratory trial of the inventory significant differences were found between groups of delinquent and normal boys, but these findings need to be checked further. Also, checks on children's perceptions with independent observations and interviews of the same parents will be needed to answer questions about the accuracy of the children's perceptions, and the possibilities of significant biases in the perceptions of certain children. Such tests are planned.

Dr. Gewirtz, who is on leave, is carrying out a program in Jerusalem, which is correlated in many ways with the studies here described. His work will permit cross-cultural comparisons on underlying constancies in infant behavior -- both the developmental aspects, and the effects of social deprivation versus enrichment on such functions as conditioning and social responsiveness and adjustments.

Section on Personality

Members of the Section on Personality have conducted research programs in three major areas: (1) Psychosomatic studies; (2) Non-content components of speech; and (3) Processes affecting cognitive restructuring. The major effort of the Section has been in the third area.

Psychosomatic Studies. Dr. Handlon has continued to work with the Adult Psychiatry Branch in their studies of emotional behavior and adrenal function. In addition to his active participation in the planning and execution of a variety of studies, he has contributed significantly to methodology by devising two techniques. The first is the Daily Mood Check List, which is self-administered. The Daily Mood Check List has been found to correlate with hormonal output as well as ward behavior. The Mood Check List has been recognized as such a reliable index of change in the individual that it has been used as an indicator of when to make hormonal determinations. Intensive studies of mood fluctuations in individuals are currently under way. These involve the utilization of an individuals's Daily Mood Check List over long periods of time. The Mood Check List has also been useful in establishing an individual's affective response base line. By an analysis of the individual's Mood Check List responses during the first and second weeks of hospitalization, it has been found possible to predict the relative hormonal levels of such an individual in subsequent weeks of the study period.

The second measure is the Defensive Maneuver Instrument. This Q-Sort has provided an opportunity to determine whether an individual's characteristic defensive maneuvers are related to the over-all level of hormonal output. This seems to be a reasonable assumption in view of the fact that it has been found that a subject appears to have his own idiosyncratic pattern of hormonal response. Such response involves not only his basal level of output but also his propensity to respond. The data analysis have not yet been completed to evaluate the effectiveness of the Defensive Maneuver Instrument.

Dr. Handlon has continued to work with Dr. Margaret Thaler-Singer to determine whether there are patterns of response to Rorschach tests which correlate with patterns of hormonal output.

Non-Content Components of Speech. The basic assumption underlying Dr. Boomer's interest in non-lexical speech is that speech mechanisms represent complex phenomena which are sensitive to and reflect transitory changes occuring in ego functioning. It is further assumed that the individual can exercise less' conscious control over the non-lexical aspects of speech than over the content per se. It is hoped, therefore, by the further development of measures and techniques that a valid index may be derived of some basic psychological processes. At the present time psychology does not have instruments to monitor the moment-to-moment transitory changes in an individual's psychological functioning. The widely used physiological indices which are presumed to relate to anxiety, arousal, etc., are open to serious criticism.

The major aspect to Dr. Boomer's research has been focused on the identification and measurement of non-content variables such as speech disturbances, rates of speech, respiration rates, etc. During the past year he has undertaken to interrelate these variables as well as correlating some speech disturbance measures with variables believed to be relevant to the psychotherapeutic process, i.e., changes in anxiety level, period of treatment, etc. In the analysis of certain categories of speech disturbances occuring in patients' communications during a prolonged period of therapy (one to two years) it was found that patients who are judged by their therapist to be making good progress revealed a striking diminution of certain categories of speech disturbances. This along with other such suggestive findings have encouraged us to undertake the development of a computer program which will permit the more rapid analysis of larger amounts of data. The data currently being analyzed include not only tape recordings of psychotherapy interviews but tapes provided by the University of Michigan of the responses of subjects under the varying post-hypnotic suggestions of "expression," "suppression," and "repression," of anxiety-laden subject matter.

Cognitive Restructuring. During the past year the work of Drs. Berlyne, Caron, and Parloff in the area of "creative problem solving" has been based on the essential assumption that central to creativity is the cognitive restructuring involved in recognizing new meaningful relationships among seemingly remote concepts and ideas.

The investigations have centered mainly on evaluating the invluence of motivational factors. Two types of motivational influences have been studied: 1. Those affecting the individual's commitment and persistence in attempting to solve a problem, and 2. Comparison of the relative effectiveness of intrinsic and extrinsic motivation. A second approach to creative problem solving has concerned the study of enhancing and inhibiting influences of different social interactions on members of dyads as they attempted collaboratively to solve open-ended problems.

Motivational Studies -- Commitment and Persistence. Dr. Daniel Berlyne conducted a series of experiments designed to investigate some of the basic processes underlying the arousal of "curiosity." It is assumed that curiosity is a prerequisite condition to creative thinking. Dr. Berlyne demonstrated that the amount of curiosity and interest evidenced by subjects was significantly related to the degree of "uncertainty" induced by confronting the subjects with sets of two and three response alternatives of approximately equal strength. He also conducted a set of experiments to determine the influence of such variables as "conflict," "novelty," "surprisingness," "complexity," and power to induce "uncertainty," on the orientation reaction. In this instance the orientation reaction was measured by the Galvanic Skin Response. All hypotheses were supported except the one concerning "complexity."

Two papers were prepared based on this work. One entitled "Collative Variables and Arousal" was read at the APA convention in September, 1960; the other entitled "Conflict and the Orientation Reaction" has been submitted for publication.

Dr. Parloff and Dr. J. Fishman, of Adult Psychiatry, have investigated the variable of "subjective probability of success" as it effects factors related to creative thinking. The aim of the study was to determine whether increasing an individual's self-confidence would enhance his "creative thinking" as measured by actual test performance on Guilford's "Creativity Factors." The technique for increasing self-confidence was hypnotic suggestion. The preliminary findings are very encouraging; however, there appears to be a condition-order effect. The individual's best test performance on any of the three matched test forms occurs under the hypnosis self-confidence suggestion condition as compared with hypnosis -- no suggestion, and the non-hypnotic

test conditions, provided, however, that the hypnotic suggestion is the first testing condition to which the individual is exposed. Efforts are now being made to determine whether this finding is due to the subject's witting or unwitting inhibition of performance on subsequent test conditions.

Motivational Studies -- Intrinsic and Extrinsic. Dr. Albert Caron conducted a study of some 1200 10th grade students in Montgomery County to compare the effectiveness of intrinsic motivation -- desire to learn because of the student's inherent interest in the topic, and extrinsic motivation -- desire to learn in order to conform to some external standard such as grades, recognition, etc. The task was to learn and comprehend some complex scientific principles and to apply them in a new test situation. The motivational states were induced by experimental manipulation of the learning conditions. In addition, such independent variables as IQ, test anxiety, need for achievement, desire for success, rish taking attitudes, and under- or over-achievement patterns were also measured. The analysis of the data has not yet been completed; however, contrary to prediction it appears that subjects in the extrinsic motivational set outperformed those under the intrinsic motivational set for both comprehension of principles and rote learning. In comparing the test performance of males and females there is some evidence that the usual finding that girls' academic performance is superior to that of boys may refer particularly to superiority in rote memory performance and not to functional understanding of abstract principles.

Collaborative Problem Solving. In recent years the need for collaborative research between individuals of different disciplines has been widely recognized; however, so many problems arise in such collaborative settings that much disenchantment has been expressed with the entire notion of collaborative or interdisciplinary efforts. A study undertaken by Drs. Parloff and Handlon investigated the hypothesis that creative problem solving in teams would be significantly affected by the degree of mutual respect existing among team members and the ability to suspend premature criticism of ideas. A replication of their earlier dyad-team problem solving study was completed this year. It appears that significantly more "good" ideas are presented under conditions of suspended critical judgment and that this suspension is more likely when the team members are mutually respectful of each other. At present we are trying to derive a model to explain the psychological processes underlying these findings.

The essential goal of research in this area remains that of learning more about the conditions and processes which underlie the utilization of one's capacities. The aim of this Section is to deal with a wide range of variables and conditions which may influence cognitive restructuring and to assess how

much of the variance each of the factors explain. To this end it is planned to further investigate some of the mediation models suggested by Hebb, Osgood, Malzman, and others. In addition the Section will continue to utilize some of the fundamental psychoanalytic concepts regarding processes underlying creative thinking. Some of the specific problems to be pursued grow out of the questions raised by the research thus far undertaken. Further, with the addition of Dr. Sanford Unger to the staff, it is anticipated that he will assist in the development of research along the lines of mediated association, manipulation of sets, and the role of affective variables on cognitive restructuring.

Office of the Chief

The Office of the Chief has, as in recent years, continued to concentrate on the psychology of schizophrenia and the nature of the therapeutic process.

In addition to participating in the current experimental program on schizophrenia to be reported below, Dr. Shakow has carried out further analysis of an accumulated body of past experimental data. Based on both groups of studies on schizophrenia, he presented a paper at the 16th International Congress of Psychology at Bonn, and is in December presenting the Collier Lecture at the University of Rochester. Aside from other values of last summer's visit to Israel, Germany, France, and England, the trip afforded Dr. Shakow the opportunity to confer with investigators who are also working on the experimental psychology of schizophrenia. He has also devoted time during the year to the preparation of a monograph on "The Impact of Freud on Psychology" which he is writing in association with Dr. David Rapaport of the Austen Riggs Center, and which is to be completed during the coming year.

Dr. Rosenthal's research has centered on various aspects of schizophrenia. Studies of the role of heredity and environment in the etiology of schizophrenia have uncovered the following points: (1) There are at least two kinds of disorder which traditionally come under this diagnostic label. In one, hereditary factors seem to be contributing almost all the variance; in the other, hereditary factors seem to account for little of the variance. (2) If one samples from among resident hospital populations, heredity will be said to account for more of the variance of the disorder than if one samples from consecutive hospital admissions. (3) The incidence of schizophrenia is no higher in twins than non-twins, a fact which rules out such a psychogenic theory of schizophrenia as "confusion of ego-identity," according to which higher incidence in twins would be predicted. (4) Concordance rates with respect to schizophrenia are higher for female than male pairs and for same-sexed than opposite-sexed

pairs of relatives when the familial relationship is primary (parent-child or sibling) but not when the familial relationship is more distant (grandparents, uncle-aunt and nephew-niece, cousin). These data strongly suggest that psychological factors are contributing at least some of the variance to the incidence of schizophrenia.

In addition to participating in the continuing studies of mental set in schizophrenia, Dr. Rosenthal has begun a new series of studies, using a battery of tests, related to cognitive and perceptual processes of schizophrenics, and in one study, of the parents of schizophrenics. The preliminary findings from these studies show: (1) In testing a small sample of parents of schizophrenics, at least one parent from each pair evidenced schizophrenic-like thought disorders, even though none of the parents had ever been diagnosed schizophrenic or hospitalized for mental illness. (2) Chronically ill schizophrenics tend not to show perceptual closure to the extent that normal subjects do. Acutely ill, recent admissions diagnosed as paranoid schizophrenic tend to show a greater amount of perceptual closure than normal subjects. (3) Although schizophrenics are more variable than control subjects on a wide variety of tasks, when they are specifically asked to vary their performance to product contrasting sized drawings (big-little), they do not vary their behavior as much as control subjects do.

With Dr. Rosenthal and Dr. Shakow, Dr. Zahn has continued investigating preparatory set and the arousal mechanism in schizophrenia using the methods of reaction time and psychophysiological recording.

In one reaction time study, schizophrenic and normal subjects were presented preparatory intervals (1"-15") of ascending and descending lengths. The findings showed that although the reaction time of the schizophrenics was approximately the same for long preparatory intervals under each condition, it improved on shorter intervals only under the ascending but not the descending condition. The normal subjects improved on shorter intervals under both conditions. In another reaction time study, the preparatory intervals were presented in an irregular ("random") manner. Under these conditions the shorter preparatory intervals produced longer reaction times than the longer intervals, a result which appears to be dependent on the previously presented preparatory interval. The effect was less in the normal subjects. A control reaction time study using varying intertrial intervals was directed at determining whether more slow pacing of events rather than maintenance of preparatory set was involved. It showed that a long intertrial interval by itself produced no appreciable detrimental effect on the reaction time of either schizophrenic or normal subjects. These results suggest that schizophrenic patients persist in a poor preparatory

set which appears to be based on a much narrower range of information than that of normal subjects. The relationship of poor set to disturbance in the arousal mechanism will soon be investigated by recording psychophysiological measures simultaneously with reaction time.

In collaboration with Dr. Hamilton, Dr. Zahn tested a small sample of schizophrenic patients at Saint Elizabeths Hospital for the effect of two phenothiazine drugs and a placebo on reaction time. The drugs appeared to improve the performance of most of the patients. However, the results were not statistically significant.

In a continuing study of psychophysiological responsivity and adaptation to visual and auditory stimuli, the GSR, heart rate, and respiration of 20 chronic schizophrenic patients were recorded and are currently being analyzed. The data from control subjects are still being collected.

Dr. Dittmann continues his work on the analysis of psychoanalytic interviews from tape recordings and motion pictures. One of the main projects has been to index these interviews in a form most meaningful for future use. At the present time some 60 interviews have been indexed -- the first 30, together with another 30 spread out over a long period -- in which 84 topics, with a minimum of overlap, and 9 time referents have been delineated.

Dr. Dittmann has completed studies of foot movement associated with speech disturbances, body movement with different moods, and judgment of mood from restricted cues, for which segments of interviews were evaluated by judges. The results from the foot movement-speech disturbance study were contradictory: in the first sample a significant positive relationship was found; in the second a negative trend showed up; and in the third there appeared no association at all. The findings from the body movement-mood study were that frequency of head movements differentiated among the moods at the .01 level of significance, while hand movements differentiated at the .001 level. The measurement of distance and duration of hand movements showed that distance differentiated at the .001 level, but duration was unrelated. Rate of hand movement was similar to that of distance. The pattern of movements in relation to mood was also analyzed, showing, for example, that the "calm" mood was accompanied by the fewest head movements and the most frequent short hand movements, while the "angry" mood was accompanied by the most frequent head movements and very few but wide-spanning hand movements. The agreement of three judges, who were presented material from silent film and filtered tapes for the judgment of mood from restricted cues was not high, although

there was no systematic bias from judge to judge. Enough questions were left open that replication with more carefully selected samples seems called for.

Dr. Dittman has also been continuing a study of judgments of affect from motion pictures which has thus far given equivocal results, primarily because of methodological problems. This study will continue, however.

During the first half of the year, Dr. Bergman worked on the clinical testing of some hypotheses derived from the "General Theory of Psychotherapy" that he had formulated last year. Counter-conditioning was the key concept of this theory. The observations made in cooperation with a goup of colleagues (Drs. Jenkins, C. Elkes, and Waskow) seemed to support the view that this direction of therapy was productive of rapid symptomatic improvements, but did not fulfill the theory's expectation of helping patients to optimal personality development. The question then arose whether the group should continue to explore the hypotheses, which were now considered limited in value in order to establish clearly these limitations. It appeared to be a job of technological and argumentative relevance, but not of theoretical and intrinsic interest. Dr. Bergman and the group, therefore, decided to turn to new hypotheses which appeared to have greater promise. He consequently dropped his plans of controlled experiments which were meant to isolate and study the process of counter-conditioning.

The new hypotheses, supported by clinical testing, are related to the current trend of experiential psychotherapy. Granting that this approach to psychotherapy has, in principle, given a workable, though not exclusive, solution to the problems of therapy, the plan is to investigate an area of extension of its practice which seems to hold intrinsic theoretical interest. The hypothesis is that the "normal" state usually achieved by successfully adjusted persons or successfully treated patients is not identical with an "ideal" state of mental health, and that this "ideal" state can be approximated by prolonged psychotherapy. Dr. Bergman and his group plan to work with subjects who are not severely ill at the beginning of the therapy. Some of the questions to which the group is seeking answers are: Can an "ideal" state free of anxiety and self-consciousness be achieved or approximated? What are its empirical concomitants in physiological, behavioral, and intellectual areas? Can everybody achiefe such a state or does it depend on certain constitutional or experiential givens?

Dr. Kendig is completing her study on the self-concept and the body image as related to disease susceptibility and organ choice. All the interviews on which the study is based were scored from the tapes by the principal investigator as they came in and 104 of these by an independent trained worker as well. On this group the inter-scorer reliability was .91. The sample, totalling 150, includes a group of 50 arthritic cases and a group of 25 leukemia cases with a like number of controls for each, individually matched on 6 variables -- race, sex, age, education, occupation, and religion. The arthritics were divided into two groups of 25 each, partly in order that statistical analysis could be begun at once on half the total, partly than an analysis of the second half could serve as a replication study. A preliminary survey of the gross pathology scores on Arthritics I showed that they did not differ significantly from those of the control group. The data were then subjected to item analysis but only 4 items showed differences significant at the .05 level. This, it was recognized, could well be by chance as indeed proved to be the case when completion of the interviews on the second group made possible comparison on these items. Item analysis on the second group of arthritics and the leukemia group is now being set up for machine processing. A design for "cluster" analyses is also being developed on the hypothesis that while the comparison of patients and controls on individual items may not be statistically significant, when related items are considered together, significant differences may emerge. For this approach 6 new scales have been developed and the scores they yield are to be analyzed with the assistance of the Computation and Data Processing Branch.

Section on Animal Behavior

The research of the Section on Animal Behavior has continued to be concerned with (a) defining the behavior served by association cortex in monkey, chimpanzee, and man (b) determining the neural mechanisms underlying this behavior and (c) specifying the neural mechanisms underlying motivation and attention in monkeys and in man. We have added to our usual techniques those of electrical stimulation and recording with very encouraging early results.

In addition to confirming our earlier findings that the chimpanzee, unlike the monkey, recovers from an initial deficit on delayed-response problems, it has been shown that this recovery may not be complete, a residual deficit persisting for as long as two years. It has also been shown that the difficulty of the delayed-response problem may be increased such that frontal-lobe lesions result in a substantial deficit from which the chimpanzee does not recover, at least within a two year period. The differences in the effects of frontal lobe lesions in the chimpanzee and monkey thus appear to be quantitative rather than qualitative.

The results of three experiments involving both chimpanzees and monkeys were consistent in showing significant impairment following unilateral prefrontal lesions. Thus, whether the measure was of learning or retention, on delayed alternation or delayed response, in monkeys or in chimpanzees, there was no overlap in the scores obtained by frontal animals and those obtained by their operated or unoperated controls. The deficit produced by unilateral frontal damage was incomplete and with sufficient training the animal's performance frequently approached control levels. These results encourage continued search for an impairment, analogous to delayed-response impairment, in man in whom the frontal injury to be studied is most usually unilateral.

An earlier study had implicated posterior mid-line structures near the splenium of the corpus callosum in delayed alternation performance. It was not clear, however, which of several possible structures were specifically involved in this behavior. Recent research suggests that it is most likely the posterior columns of the fornix.

An intensive analysis of the problem-solving behavior of monkeys with frontal lesions has led to the hypothesis that their impairment is due to abnormally strong perseverative tendencies. The hypothesis provides a consistent account of the frontal animal's difficulty on learning set, discrimination reversal, and one-trial discrimination learning. Even more important, however, the hypothesis offers an alternative account of the frontal animal's deficit on the delayed-response test, a deficit which has

been traditionally ascribed to a "loss of recent memory." This latter conception has faced many difficulties, among which has been the failure of a recent study (in which this section collaborated) to find any evidence of memory loss after frontal-lobe injury in man. Conversely, the "perseveration" hypothesis appears to be consistent with a large body of evidence pertaining to the effects of frontal injury in man.

While the "perseveration" hypothesis is thus seen to be potentially useful in ordering a large literature on the effects of frontal-lobe damage in both man and animals, it is recognized that the conception is not yet sufficiently precise. A number of on-going experiments give promise of leading to a sharper definition. For example, that perseveration must be distinguished from loss of inhibition is suggested by the results of experiments in which animals with lateral frontal lesions are compared with animals in which orbital frontal cortex has been removed. On tasks which demand inhibition of food-getting responses, the orbital animals generally perform more poorly; on tasks which demand frequent switching between responses, the lateral frontal animals perform more poorly. Further investigations along these lines may be expected to yield still sharper distinctions between perseverative tendencies and superficially similar defects.

A detailed picture is beginning to emerge of the nature of the interaction between the primary visual and inferotemporal areas. Having already demonstrated that the two areas are interconnected by ipsilateral and contralateral pathways (the latter crossing in the posterior third of the corpus callosum), the work in the past year has attempted to determine whether these connections are direct or indirect, and, if the latter, what intermediate cortical areas are involved. Both neuroanatomical and behavior-ablation experiments agree in implicating prestriate and parietal areas as intermediate relay stations along the striate-inferotemporal pathways.

It has been demonstrated in other recent experiments that the visual impairment which is produced by severing these pathways is not simply a by-product of visual field defects. The impairment thus appears to be qualitatively similar to that produced by bilateral inferotemporal lesions. However, the nature of this associative defect in vision still eludes precise definition. Further studies aimed at distinguishing between two possible interpretations - one following a perceptual model, the other a conditioning model - are currently underway using stimulus generalization techniques.

Section on Animal Behavior (Cont'd)

While the research outlined above has provided a sound rationale for ascribing visual functions to the inferotemporal cortex, other studies, from this laboratory and elsewhere, have reopened the issue as to whether the functions served by inferotemporal cortex are exclusively visual, or whether they embrace olfactory functions as well. A study aimed at precise localization of the temporal-lobe region serving associative functions in olfaction is now in progress. Similarly, recent studies have suggested that frontal association cortex may be implicated in auditory functions, thus reopening the issue as to whether or not frontal cortex serves specific sensory functions. A study aimed at re-examining this question is now in progress.

Electrical stimulation and recording techniques are being used to construct a volumetric map of areas in the forebrain of the monkey which affect food and water intake. To date, using six animals, approximately 3000 points have been explored. Food and water ingestion and food (and possibly water) ejection can be elicited and localized separately, each from many points in the forebrain. The most effective of these points are selected for chronic studies in which each point is evaluated from the standpoint of motivating self-stimulation and escape behavior, autonomic effects, and such interrelated effects as facilitation, inhibition, and transmutation. Remote stimulators and telemetric devices are being developed to enable assessment of these effects in animals in a free-ranging situation.

Points have also been localized from which aggression or penile erection may be evoked by electrical stimulation. Modest success has been achieved in conditioning these behavior patterns by using classical conditioning procedures. However, many artifacts confound the results making conclusive statements unwarranted at this time. Nevertheless, the early successes are extremely encouraging and suggest that these evoked responses can be conditioned. In connection with these stimulation studies a technique for localizing electrodes in the brain was developed. This method is based on the fact that the impedance between an exploring intracerebral electrode and some other fixed point changes in a consistent fashion as the electrode is advanced through the brain. If one knows from a stereotaxic atlas what structures are likely to be encountered in an electrode track, close monitoring of impedance changes as the electrode is moved can signal precisely the passage of the electrode tip into a given target. Also, a very compact pulse-subtraction amplifier has been developed making it rather easy to monitor a variety of signals from an animal while he is in the stimulating circuit.

Section on Animal Behavior (Cont'd)

The studies of attentive behavior in man have been concerned with comparison of behavioral and physiological concomitants of impaired performance and with description of the nature of the behavioral impairment. The information which is now available indicates certain similarities and differences among the effects of the various agents that have been studied which appear to have significance for the specification of the central mechanisms necessary for consciousness and wakefulness. Thus, although sleep deprivation, acute chlorpromazine administration and petit mal epilepsy all produce marked impairment in the performance of tests of sustained attention, only sleep deprivation and petit mal epilepsy can be characterized to any significant extent as showing simultaneous changes in the EEG. The fact that the behavioral changes may occur independently of the EEG changes (i.e., with chlorpromazine) would seem to imply separate neural regulation of these phenomena and, possibly, independent neural systems. Although the effects of sleep deprivation and petit mal epilepsy are similar in the correspondence between behavioral and EEG changes, they too differ, but with respect to the autonomic accompaniments of the period of impaired responsiveness; opposite peripheral circulatory changes accompany the two states. This suggests further specificity and complexity within the underlying neural regulatory systems. The notion of independent systems subserving behavior and EEG changes receives additional support from the analysis of the time relations between changes in behavior and EEG changes in petit mal epilepsy. Evidence has been gathered which indicates that the behavioral impairment accompanying the spike and wave burst characteristic of this disorder precedes the burst in time and begins to subside before the burst has ended. Other information suggests that the perceptual and motor aspects of the attention deficit may have differing time courses. These out-of-phase relationships may be interpreted as indicating separate, although closely related systems being affected differentially in time by some central epileptogenic process. In the coming year these studies will be directed in part towards further analysis of the relationships among behavioral, EEG and autonomic information. Other research will attempt to specify and contrast the nature of the deficit in petit mal patients and in normal subjects under the influence of centrally-acting drugs using appropriate normal and neurological patients as controls. In addition, a study is currently under way in which direct brain stimulation of trained monkey subjects will be carried out, simultaneous with performance on an attention test, in an attempt to test directly hypotheses concerning the differing neural systems underlying the regulation of behavior, EEG and autonomic functions.

Participating in various aspects of these studies have been Dr. H. E. Rosvold, Chief of the Section, and Drs. M. Mishkin, A. F. Mirsky, M. K. Szwarcbart, and B. W. Robinson. Also participating have been Dr. Charles Butter, NIMH Post-Doctoral Fellow, Dr. Stefan Brutkowski, a Visiting Scientist from Warsaw, Dr. H. Kuypers of University of Maryland, as a Consultant in Anatomy, and Mr. Thomas Brown, NIMH Pre-Doctoral Fellow.

Section on Perception and Learning

The Section on Perception and Learning has two quite separate areas of research -- that of Dr. Calhoun at Rockville and that of Dr. Carlson on perception.

Rockville Farm Project. This year saw the completion of Dr. Calhoun's first pilot studies begun in 1958 and the initiation of a further series oriented toward evaluating factors which have emerged as major variables in the pilot studies. Dr. Calhoun, with the assistance of Dr. Barbehenn, post-doctoral fellow, has studied the effects of several different physical structures of the environment on socially-relevant aspects of the behavior of rats.

In an environment where movement patterns had been biased to favor one sub-area over others, abnormal aggregations of animals developed. As much as 80% of feeding activity, for example, occurred in that sub-area, even though all sub-areas would meet the requirements of basic needs equally well. Paralleling the development of this abnormal aggregation, normal patterns of maternal, nest-building, and sexual behavior became disrupted, and adult females experienced a high rate of mortality due to reproductive abnormalities. Liver and serum analysis suggested that these and other symptoms might be due to Vitamin A dysfunction. By varying the degree of prior opportunity to adjust to strange stimuli and the number of new stimuli in a test field, it appeared that fewer prior opportunities for adjustment led to greater avoidance of the test field and, for those rats entering the test field, hyperactivity persisted longer with greater numbers of strange stimuli.

As a consequence of these and other results a factorial study has been initiated involving large and small social groups, different levels of Vitamin A in the diets, and stressful and non-stressful conditions. Large-scale groups appear to offer more opportunity for adjusting to new situations; an increase in Vitamin A, however, may work in the opposite direction, decreasing the ability of rats to adjust to change.

This year has also seen the completion of a long-term study begun by Dr. Calhoun in 1946 on the evolution of social groups among mammals. He has elaborated a general formulation on this topic, tracing interactions in space which successively lead from random distribution with poor communication, to gradually condensing groups with mean size of twelve individuals and enhanced communication, to herd-type animals living in large groups and capable of reducing or ignoring communication among associates. This formulation has been made possible through data contributed by a number of field workers, who have executed studies under Dr. Calhoun's direction.

Perception. The dichotomy between sensation and perception has been a source of fundamental difficulty since the beginnings of experimental research in perception. It is manifested in many ways in present-day perceptual theory, especially with respect to the problem known as object-constancy. Perceived object-size remains functionally invariant with varying object-distance in spite of the fact that retinal image-size varies inversely with distance. The general resolution of this apparent discrepancy has been to assume that the primary sensory datum is the angular size of the retinal image, which is integrated perceptually with other elementary cues to object-distance, perceived object-size emerging as a complex, judgmental result. One of the most compelling supports for this view is the observation that physical extents, immediately and directly, 'look' smaller as they are farther removed from the observer. It is readily verified by most observers, for example, that railroad tracks appear to converge in the distance.

Dr. Carlson has formulated an alternative hypothesis, which postulates that veridical size-perception is the basic perceptual fact and seeing-in-perspective is a culturally conditioned, attitudinal bias. Two experiments were completed during the year which offer strong support for this argument. In the first, experimental judgments of overestimation of size-at-a-distance were shown to be a function of non-perceptual factors. In the second, it was demonstrated that administration of the centrally-acting drug LSD produced underestimation of size-at-a-distance only when the drug condition represented the subject's first experience with the experimental task. This result can only be interpreted as an interaction between drug effect and response-bias, not as a direct effect of the drug on the perceptual process itself.

Another fundamental problem in perception is concerned with perceptual adaptation to motion. Theoretical accounts of this phenomenon have generally treated it as analogous to color or temperature adaptation. By means of an aftereffect experiment, Dr. Carlson has obtained results suggesting that this analogy can only be partially correct. The zero-point of perceived velocity was shifted appropriately as a function of adaptation; but there was no effect of adaptation to a given velocity on a subsequently experienced velocity of opposite direction, a kind of aftereffect which occurs rather strikingly in color and temperature perception.

A special test for measuring perceived velocity has been developed in connection with the foregoing velocity adaptation experiments. The essential feature of this test is that response time is utilized as a correlate of perceived velocity. Dr. Feinberg, of the Clinical Neuropharmacology Research Center, and Dr. Carlson, in an initial exploration of the response of schizophrenic patients to this test, discovered that schizophrenics appear to manifest extraordinarily long response times while at the same time reacting appropriately to variations in the stimulus parameters of the task. A larger scale study has been set up at St. Elizabeth's Hospital to evaluate this preliminary finding, and collection of the data is nearing completion at the present time.

Section on Aging

The program of the Section on Aging is directed at securing, through experimental investigations of the behavioral capacities and physiological status of animals and humans, an understanding of aging as a pervasive natural phenomenon. Through the research and theoretical efforts of the staff members of the Section the subject matter has undergone what, in retrospect, seems to have been a rapid transition from a descriptive naturalistic phase into a more tightly organized state of knowledge. Though it has several facets, the research program of the Section has two principal foci: (1) the accumulation of systematic information concerning behavioral and physiological changes associated with age, (2) the systematic investigation of age-related impairments of the higher cognitive processes in man, and the study of possible methods of preventing or overcoming such deficits. Work has continued on the analysis of age changes in learning ability and the speed of psychological processes. The cellular components and extracellular relations in the nervous system have also continued to be studied in the hope of identifying some of the biological concomitants of the behavioral changes in aging.

Eleven of the fifteen chapters planned for a monograph reporting the results of the extended, interlaboratory study of aging have been completed, and publication has been scheduled for the spring of 1961. In collaboration with several laboratories at NIH, the Section on Aging also has in progress a set of follow-up studies on the survivors of the group of aged subjects from whom the original data for this study were obtained during 1955-1957. Selected reports on work presented in the seminar at Berkeley and at the meetings of the International Congress of Gerontology in San Francisco will be collected into two volumes that are being prepared for publication early in 1961.

Dr. Birren reported at the Berkeley seminar on preliminary results from his and Dr. K. Riegel's response time study of age-differences in primarily mental activities as compared with predominantly motor performances. In this experiment, a set of 22 problems, programmed by the Psychomet and differing widely with respect to their demands on associative facility, were administered to two contrasting age groups. The results indicate that the relative speed-impairment associated with aging increased as the complexity of the mental functions required by the problem increased. The apparent age-decrement in speed of performance on tasks requiring such mental operations as color-symbol matching, superordinate, coordinate and part-word association far exceeded that which could be understood in terms of the purely motor deficits found in analogous tasks that did not require these cognitive functions. During the current year, data will be obtained from additional subjects and the full set of

results will be analyzed to determine the relative variances contributed by the associative processes that are found to deteriorate with age.

Dr. Birren, using a two choice point water-maze, has continued his study of age-differences in the psychomotor performances of rats. The initial learning portion of this experiment has been completed and the results show no dramatic effect of age on learning proficiency. The animals will now be retrained on the same maze after a six-month interval without practice. Having satisfied a relearning criterion, they will be given a new problem. Learning under these interference conditions will then be measured. When this study is completed, the Section on Aging will have available for comparison four sets of data, obtained under a variety of conditions by different experimenters, all relevant to the study of the effects of age on learning efficiency and interference. Coordinated analyses of these results are expected to provide rather precise identification of conditions conducive to the occurrence of age-differences in the learning ability of rats.

Dr. Botwinick's comparison of the reaction time of young and old human subjects in relation to set and sense modality has continued. 64 young controls and 15 elderly subjects have already been tested, and 49 elderly subjects in good physical condition are to be added to the group. The results obtained thus far indicate that changes of the reaction time response and the ability to maintain set are associated with the aging process.

Four papers are in preparation by Dr. Jerome on related studies of learning and transfer of training in senescing rats. They provide evidence to the effect that (1) aging animals are not more stereotyped in their free choice behavior than are young adults, (2) they do not manifest a greater tendency to higher order (sequential) stereotypes, (3) senescing animals, under some conditions at least, learn as rapidly as young adults and (4) aging animals transfer their learning about as efficiently as younger ones. A collaborative study with Drs. Goodfriend and Kaufman is in progress on the effects on learning of several phenylalanines, possible causative agents of phenylpyruvic oligophrenia. Additional collaborative work is being carried forward with Dr. Streicher in screening a set of drugs for differential age effects on behavior.

The results from Dr. Jerome's study of the effects of aging on the higher cognitive processes in man reflect a marked impairment of the heuristic controls relevant to the solution of the set of problems programmed by the Logical Analysis Device. Though there were marked individual differences among the old subjects, even the best

of them was not as proficient as the worst of the young subjects. The following specific deficits were prominent in the performance of the aged: (1) failure to secure a clear indication of sub-goals before engaging in random search, (2) failure to take advantage of mnemonic aids urged upon them by the procedure, (3) inability to develop solution strategies designed to reduce the cognitive strain of the problem solving effort, (4) inability to apply solution strategies that were repeatedly explained, (5) failure to draw inferences appropriate to information at hand. These results have emphasized the urgency of investigating the feasibility of retraining in the basic heuristic processes that appear to have so seriously deteriorated in the process of aging.

Employing an original technique in which a single word or single phrase is played repeatedly to the subject from a loop of recording tape, Dr. Warren has made a comparison of the perceptual processes of old and young adults. This repetitive stimulation gives rise to illusory perceptual changes frequently involving considerable phonetic distortion. Young and old subjects differed markedly in their reactions to this type of presentation, the illusory transitions occurring about four times more rapidly in the young than in the old. In the older subjects, moreover, the stimulus word's frequency of occurrence in English appeared to influence the illusion more than it did in the younger subjects, the latter appearing to give greater emphasis to phonemic aspects of the stimulus. It appears therefore that the manner in which stimuli are organized perceptually changes with age--increasing reliance on the probability of occurrence and increasing perceptual stability being associated with age.

Dr. Streicher's investigation of the thiocyanate space of various rat organs and tissues was terminated this year. For the brain the extracellular space was found to be a function of dosage. The extrapolation of the curve relating extracellular volume to plasma level indicated a space approximately 2 to 5 percent in young and old animals alike, whereas for other tissues, heart, skeletal muscles, testes and kidney of senescent animals showed significant increases in extracellular volume. There was, however, some evidence that thiocyanate was eliminated from the brain of older animals more slowly than it was from the younger. Finally, animals in which cerebral edema was induced experimentally showed no change in the distribution of thiocyanate, although the sodium content of the brain was elevated 50 percent and that of the spinal cord approximately 100 percent. From these studies it was concluded that if such hypothesized age-related changes in the brain as loss of cells, dehydration, gliosis, etc., occur in the rat, they are not reflected by alterations in the extracellular space which serves as a sensitive

indicator for similar changes in other organs. Dr. Streicher, in collaboration with Dr. Rall of the Laboratory of General Medicine, NCI, and Dr. Patlak of the Section on Theoretical Statistics and Mathematics, NIMH, has also undertaken an investigation designed to identify and measure the rates of those processes which are responsible for the movement of charged, lipid-insoluble material into and out of the cerebral spinal fluid. Preliminary results indicate that the rates of entry of some materials are a function of their concentrations in the blood plasma. More detailed conclusions will be available when the mathematical analyses are completed.

The several lines of investigation being explored by the Section on Aging are providing accumulating evidence to the effect that the cognitive processes of lower animals are only slightly, if at all, impaired by age. This raises doubts about a commonly accepted assumption that the deterioration of the mental capacities in man with age is an intrinsic component of an ontogenetically determined process characteristic of all biological levels. Similarly, though our physiological studies have revealed age-related deteriorations in several classes of tissue, the differences observed would explain deficiencies in reproductive, vegetative and motor activities more directly than they would impairments of tissue more directly connected with mental capacities. Diligent search in our own laboratory and elsewhere has failed to uncover any convincing evidence of cortical or sub-cortical degeneration of neuronal materials. This may be interpreted as not consonant with a position that the intellective faculties of man are structurally predestined to degradation with age. From the study of human subjects, the evidence of impairment of the perceptive processes combines with consistent indications of an age-related decrement in the speed of reaction to suggest a curtailment of interactive capacities. This in turn explains, to some extent at least, the observed deficit in associative facility, since a decrease in interaction would naturally entail associative disuse. Some appreciable decrement in the ability to deal with problem situations is, of course, to be anticipated from a curtailment of interaction and a reduction of association facility. But the marked collapse of the elementary heuristic system appears to suggest a more pervasive failure for which one would have to invoke a theory of generalized decay of organization at the neuronal level. At the level of heuristic regulation, the relevant organization, as distinguished from gross architectonics, could reasonably consist of a delicate tuning of synaptic resistances and dendritic elaborations too subtle to be detected by biochemical analyses. According to Hebbian theory, such regulation is originally generated by prolonged

training and is maintained only at the expense of assiduous exercise, so that reduction of interaction would potentially result in a decay of organization sufficient to explain the phenomena of cognitive impairment commonly observed in experiments with the aged. The Section on Aging will probably continue to direct much of its future work toward the search for specific age-related deficits, both behavioral and physiological, and toward the determination of the extent to which the heuristic deterioration commonly associated with aging can be modified. It is expected that from such studies of modification, additional important principles of the aging process will be uncovered.

Annual Report, January 1 through December 31, 1960
NIMH -- Laboratory of Clinical Science
Seymour S. Kety, Chief

The Laboratory of Clinical Science has continued in its attempts to bridge the research areas between the basic biological disciplines and the problems of clinical psychiatry. The Laboratory represents a group of scientists and their associates, organized into sections representative of various biological and clinical disciplines, who pursue both independent and collaborative research relevant to mental illness. Their motivations and interests are strongly committed to the internuncial position which the Laboratory occupies in the Intramural Program, either by virtue of their own medical and psychiatric backgrounds or their experience and willingness to participate in a clinically oriented program. Because of the highly collaborative aspect of much of the research in the Laboratory, the program is perhaps better outlined in terms of problem areas rather than by listing the contributions of the various sections. This report is, however, based upon original reports prepared by the various section chiefs:

Office of the Chief
Unit on Schizophrenia
Elwood H. LaBrosse

Unit on Psychosomatics
Philippe V. Cardon, Jr.

Section on Medicine
Roger K. McDonald

Section on Physiology
Edward V. Evarts

Section on Psychiatry
William Pollin

Section on Biochemistry
Marian W. Kies

Section on Cerebral Metabolism
Louis Sokoloff

Section on Pharmacology
Julius Axelrod

SCHIZOPHRENIA RESEARCH

A current hypothesis relating to the pathogenesis of schizophrenia has postulated a defect in the metabolism of epinephrine in this disorder with the production of certain abnormal derivatives which may account for the major symptoms of the disease. This hypothesis was developed at a time when the knowledge of normal metabolism of epinephrine was extremely vague and it was possible to account for only a few percent of the epinephrine released in the body, this being the epinephrine which was not altered by body metabolism but was excreted in the urine unchanged. In order to test this hypothesis in schizophrenia, it was first necessary to learn the normal pathways of metabolism. This, Dr. Julius Axelrod was able to do in a program of activities extending over the past several years so that in normal animals and man it is now possible to account for practically all epinephrine administered and also that presumably

produced in the body in the form of two major metabolites, metanephrine and 3-methoxy-4-hydroxymandelic acid, and four minor metabolites including unchanged epinephrine. Based upon this work, Dr. Elwood LaBrosse and his associates in the past year have completed a definitive study of the metabolism of circulating epinephrine in a group of schizophrenic patients. The metabolites in this population were found to be qualitatively identical with that in the normal population with no evidence for the presence of abnormal metabolites. Only one compound, 3-methoxy-4-hydroxyphenylglycol, was excreted to an extent significantly different from that in normal volunteers (8.9% as opposed to 7.1%). This study argues against the presence of a major abnormality in the metabolism of circulating epinephrine in this disorder.

One of the interesting positive findings recently reported in a major segment of schizophrenia is that of Frohman and Gottlieb at the Lafayette Clinic, which suggests the presence in plasma of such patients of a factor which alters the carbohydrate metabolism of red cells. In the past year the Laboratory provided an opportunity to Dr. Frohman to apply his test to schizophrenic patients and normal volunteers on our wards and to carry out the appropriate analyses in this Laboratory. On the basis of blood samples submitted to him from twelve schizophrenic patients and eight normal volunteers and carefully coded to prevent their identity from being known, it was possible on the basis of his findings to predict correctly in a highly significant number the presence or absence of schizophrenia. On the basis of quite a different approach, Dr. Peter Mueller of the Unit on Psychosomatics, studying the response of free fatty acids to insulin, has found a reproducible alteration from the norm in a significant number of schizophrenic patients. These studies are being actively pursued with a systematic consideration of the many variables involved in an effort to determine to what extent either of these findings is basic to or characteristic of a subgroup of schizophrenic illnesses or is the result of adventitious factors.

In the family study area, a pilot study phase was completed by Dr. William Pollin and the Section on Psychiatry and a study of matched groups of families has begun. The emphasis continues to focus on an effort to use comparison of a schizophrenic patient and his non-schizophrenic sibling within the same family as an approach deemed likely to provide the maximal information concerning what types of emotional relationships and life history events may be related to the onset or course of schizophrenic illness. In the pilot study phase substantial differences were judged to be present in 8 of 10 families which seemed relevant to the appearance of schizophrenia in one child and its absence in his studied sibling. The matched study now beginning will compare differences in family

relationships and life history events in one group of fifteen families where one of the children is schizophrenic and another is not, and in a matched group of fifteen other families where one child is juvenile delinquent and the other is not, in an effort to answer the question: Which, if any, of the characteristics present in the families of schizophrenics and predominantly present in the life of the schizophrenic child, in comparison with his non-schizophrenic sibling, are actually unique to schizophrenia?

ROLE OF THE BIOGENIC AMINES IN MENTAL STATE

One of the most interesting aspects of modern neurochemistry has been the finding that a number of amines with rather potent pharmacologic effects elsewhere in the body are differentially localized in various parts of the brain. These include norepinephrine, serotonin, tryptamine, histamine, among others. The distribution of these substances in certain functional areas of the brain and the alterations in their concentrations which occur in association with the action of potent psychotropic drugs such as reserpine or iproniazid, have suggested that these agents play an important role in normal behavior or may even be implicated in schizophrenia. Although the synthesis, destruction and levels of these compounds in brain can and have been measured in animals and correlated with behavioral state, no such direct approach is possible in man for ascertaining the possible role of these substances in mental state or in the highly specialized behavioral patterns of normal and schizophrenic human beings. Studies in the blood or urine may serve to detect general abnormalities in the metabolism of these agents if they occur but are not sufficiently sensitive to elucidate their specialized metabolism in the brain. An ingenious technique based upon double-labeling has been devised by Dr. Irwin Pin, which theoretically appears capable of yielding information on the brain metabolism of biogenic amines from studies of blood and urine, but numerous methodological problems remain to be solved before it can be applied to man.

Another approach has been carried out by Drs. William Pollin and Philippe Cardon, in which other members of the various sections have also participated. It employs the dietary or parenteral administration of certain known precursors of these and other amines in substantial amount, aided by the administration of drugs which inhibit monoamine oxidase and which would be expected to retard the destruction of brain amines and increase their concentration. Careful behavioral and psychiatric observation of patients under such conditions may serve to elicit mental or behavioral changes which may be characteristic of alterations in specific amine levels. In the course of the past year, there has been an opportunity to test a number of amino acids, including tryptophan, phenylalanine, histamine,

glutamine, tyrosine, glycine and methionine, and two more immediate precursors of norepinephrine and serotonin. When approximately ten times the normal dietary content of these amino acids is administered in successive studies, each for a period of one week, two of them were associated with significant behavioral change in a segment of the patients. Methionine was associated with increased activity and alertness, and an accentuation of some of the specific schizophrenic symptomatology which was followed by what appeared to be a moderate quiescence of certain symptoms in a number of the patients. Tryptophan, especially in conjunction with the monoamine oxidase inhibitors, produced a relaxation of inhibition and a freeing of association where these had been abnormally marked in several patients. These findings are being further evaluated in order to elucidate their significance to the nature of schizophrenia and the relationship of biogenic amines to behavior.

FAT METABOLISM AND THE NERVOUS SYSTEM

Drs. Peter Mueller and Philippe Cardon have been conducting a study of the relationship between plasma-free fatty acids and the nervous system. These substances represent the form in which, to a considerable extent, fat is mobilized from adipose tissue and transported in the blood stream. A number of interesting findings have come to light which appear to have special relevance to mental or neurological disease. It was found that vitamin C appears to be necessary for the mobilization of fatty acids which occurs in response to fasting. It was also found, in conjunction with Dr. Kies, that guinea pigs in which experimental allergic encephalomyelitis had been induced showed a marked increase in free fatty acids. When vitamin C was withheld and the animals became deficient in this vitamin, the appearance of the encephalomyelitis was entirely prevented. After restoration of the normal diet, the guinea pigs retained their resistance to the first and to a second inoculation with antigen.

METABOLISM AND INACTIVATION OF DRUGS AND HORMONES

Peripheral Metabolism and Inactivation of Catecholamines.

This chemical group includes epinephrine and norepinephrine as substances of considerable biological and psychiatric interest. Dr. Julius Axelrod and his collaborators in the Laboratory have delineated the significant features of the metabolism of norepinephrine in the body and have demonstrated a number of areas in which the metabolism differs quantitatively from that of epinephrine. In addition and of considerable interest has been the work on mechanisms of binding and inactivation of norepinephrine at or near its site of action. Using tritium-labeled norepinephrine of high specific activity,

they have demonstrated a rapid uptake of this hormone following its injection into animals by certain tissues of the body which are richly innervated by the sympathetic nervous system. Denervation of such structures results in a loss in the ability to bind norepinephrine, and a number of drugs, including reserpine, chlorpromazine, amphetamine and cocaine, have the ability to prevent this binding or to cause the release of bound norepinephrine from these sites. The tranquilizers, reserpine and chlorpromazine, although having similar clinical effects have very few chemical ones in common, and this similar action on norepinephrine may represent an insight into the mechanism of their ataractic action.

REGIONAL NEUROCHEMISTRY

In the recent past neurochemistry has moved from a consideration of over-all aspects of cerebral metabolism to a recognition of the remarkable heterogeneity of the brain and the relationships between regional neurochemistry and the specialized functions of the nervous system. As an indication of the growth of interest in this area, it may be mentioned that the Organizing Committee of the International Neurochemical Symposia chose as the topic for the Fourth Symposium, held in the summer of 1960, "The Regional Chemistry, Physiology and Pharmacology of the Nervous System," the program of which the Chief of this Laboratory was asked to organize. A number of investigators in the Laboratory have contributed significantly to this field.

N- and O-Methyl Transferases in the Nervous System. Dr. Julius Axelrod has continued his investigation of these enzymatic processes which appear to be concerned with the interconversions of a number of substances present in the central nervous system and by means of which their activation or inactivation may be achieved. Imidazole-N-methyl transferase (an enzyme responsible for the methylation of histamine) and catechol-O-methyl transferase (responsible for the enzymatic inactivation of catecholamines) were found to be present in all areas of the central nervous system. The highest concentration of the histamine-methylating enzyme was found in the neurohypophysis while catechol methylation was highly localized in the adenohypophysis. The discovery of the histamine-methylating enzyme in brain, by Drs. Donald Brown and Julius Axelrod in 1959, in concentration higher than that in any other tissue is very suggestive of an important and as yet unknown role for histamine in the central nervous system.

Synthesis and Degradation of Melatonin. The pineal gland, a small structure directly in the center of the brain, has challenged the imagination of scientists even before the days of Descartes. Its function to date is unknown. Recently,

Dr. Lerner at Yale Medical School isolated an agent, melatonin, which appears to be highly localized in the pineal gland, which structure alone in the brain has the ability to synthesize it. Drs. Julius Axelrod and Irwin Kopin of this Laboratory, with the collaboration of Dr. Herbert Weissbach of the National Heart Institute, have demonstrated the mechanism of the synthesis of melatonin by enzymes found in the pineal gland. These enzymes effect the acetylation and methoxylation of serotonin with the production of melatonin. The distribution of melatonin after it is formed is to all tissues including the brain, and its degradation is mainly by 6-hydroxylation with the excretion of the hydroxylated compound in the urine and bile. The function of melatonin in the brain is at the present time unknown, although in lower animals it is known to be the most powerful melanocyte-contracting substance known. The relationship between these cells which control pigmentation in lower animals and brain function is obscure.

Isolation of Antigenic Protein from Myelin. The Section on Biochemistry under Dr. Marian Kies has been engaged in a long-term program on the biochemical aspects of experimental allergic encephalomyelitis, a disorder produced in guinea pigs by the injection of suitably treated brain extracts. This disorder serves as a useful animal model of clinical demyelinative diseases, of which a specific example is multiple sclerosis. In previous years Dr. Kies has succeeded in isolating from brain extracts a purified protein which appears to be the antigenic agent. Since myelin is the part of the central nervous system which is specifically damaged by the host's reaction to the antigenic protein, it has been assumed but not demonstrated that the protein was located in myelin. Convincing demonstration of this was achieved during the past year. Dr. Robert Laatsch, working with Dr. Kies, has isolated an active protein from purified myelin. Like the antigen prepared from whole brain, it is antigenic at levels from 1 to 5 μg and has similar physical characteristics. Dr. Kies has continued to pursue the provocative finding of the previous year that the water-soluble protein antigen is capable in itself of suppressing the behavioral and histological manifestations of the disorder. An understanding of the mechanism of this suppression may have some relevance to the ultimate prophylaxis or therapy of similar demyelinative processes in man.

MECHANISM OF ACTION OF THYROXINE

Dr. Louis Sokoloff and the Section on Cerebral Metabolism have concentrated their activities in the past year in a further definition of the significant finding of an action of thyroxine on protein synthesis, directed toward an elucidation of the mechanism of this stimulation. It has been conclusively established that mitochondria are essential for the thyroxine

effect, but the actual effect is the stimulation of amino acid incorporation into protein. In addition, there is also need for an oxidative phosphorylation system. Although energy derived from glycolytic processes appears adequate to support amino acid incorporation, the thyroxine stimulation is observed only when the energy is provided by oxidative phosphorylation. The work gives a basis for postulating the formation of an intermediate which then stimulates the amino acid incorporation. The intermediate has not thus far been identified, but it is planned to emphasize this aspect of the project during the coming year. Efforts have been directed in the past year toward demonstrating the relationship between the effect on protein synthesis which was observed and the physiological action of thyroxine. Studies with thyroidectomized rats have confirmed the expectation based on such a relationship of a decreased rate of amino acid incorporation. Studies with various analogs of thyroxine have also indicated a parallelism between physiological activity and effectiveness on the amino acid incorporation system.

NEUROPHYSIOLOGY

Dr. Edward Evarts and the Section on Physiology have continued their definitive studies of the activity of single neurons in unanesthetized cats during sleep and wakefulness. There appears to be a greater differentiation of neuronal activity during waking than during sleep. Neurons in the reticular formation show a reduction of evoked responses during sleep together with an increase in spontaneous activity. Neurons here and in the visual cortex show an increase in the ratio of evoked to spontaneous activity during waking. This may explain the increase in sensitivity to environmental stimuli which appears to occur during the waking state.

Studies of evoked potentials in man, made possible by the development of an improved evoked response detector by Mr. Robert Cox, have been carried on in normal subjects during sleep and wakefulness. These have indicated that sleep leads to an augmentation of the initial phases of cortical response to retinal stimulation and to disappearance or reduction of the latter phases of the response. Preliminary studies in schizophrenic patients have failed to reveal any abnormalities of evoked potentials.

NEW TECHNIQUES

One of the important accompaniments of human stress is the release from the adrenal gland and the sympathetic nervous system of the important hormones, epinephrine and norepinephrine. Although measurement of the amount of such release and its correlation with other measures of stress in health and disease is a much sought after bit of information, the available

techniques for deriving such information have been quite unsatisfactory, depending upon analysis of the urine for epinephrine or norepinephrine which are excreted unchanged in the amounts of only a few percent of that which is released. Since more than 95% of these hormones are converted to other substances after their release, any attempt to estimate the amount secreted from an analysis of this extremely small residue is associated with error which may be several hundred percent in magnitude. On the basis of new knowledge acquired by Dr. Axelrod in this Laboratory and other investigators elsewhere, the metabolic products of these catecholamines have now been identified. Mrs. Virginia Weise, working with Dr. Roger McDonald, has in the past year developed a technique for the determination of 3-methoxy-4-hydroxymandelic acid (VMA) in the urine of man. Since this compound in the urine accounts for some 40% of injected and presumably endogenously produced epinephrine, it is a much closer indicator of catecholamine secretion in various states. These workers have begun to apply their method in a number of clinical states and have found, for example, that there is a high excretion rate in patients with involutional depression and that certain drugs or procedures, like reserpine or electroshock, cause marked increases in VMA excretion.

Monoamine oxidase inhibitors constitute a class of drugs which have been utilized in the treatment of depression. In evaluating the enzymatic effectiveness of various members of the group under clinical conditions and in order to monitor dose levels, it is of some importance to have available a measure of the degree of enzymatic inhibition under clinical conditions. Measurement of the excretion of tryptamine, suggested by investigators at NHI, has served as a useful procedure. This excretion, however, is not only a function of monoamine oxidase inhibition but also that of dietary tryptophan intake. Drs. Irwin Kopin and Elwood LaBrosse, utilizing the knowledge that indole acetic acid excretion is also proportional to dietary tryptophan, have suggested and used the ratio of tryptamine to indole acetic acid excretion in patients under iproniazid treatment. This ratio appears to be a better index of monoamine oxidase inhibition than the tryptamine excretion alone.

For many years it has been possible to record electrical activity evoked from the cerebral cortex of animals by auditory or optical stimuli through electrodes placed directly on the exposed cerebral cortex. In intact man, such signals, having to penetrate the skull and scalp, are lost in the background noise of the electroencephalogram. Although a few other groups have found it possible to extract the evoked waveform from the background noise in human recording by a system of algebraic addition of repeated responses, the techniques available have been extremely complex and prohibitively expensive, or quite

cumbersome. Mr. Robert Cox, working with Dr. Evarts, has developed an evoked response detector which appears to be able to carry out this averaging process effectively and neatly at a relatively small cost, making possible the more widespread utilization of such studies in electroencephalographic laboratories.

Summary Report

Calendar Year 1960

Laboratory of Socio-environmental Studies

Melvin L. Kohn, Acting Chief

Dr. John A. Clausen, Chief of the Laboratory since its inception in 1951, has left the National Institute of Mental Health to become Director of the Institute of Human Development at the University of California at Berkeley. Dr. Clausen created de novo what was at first a small program of applied sociological research and what later broadened and deepened into a far-ranging basic research program in sociology, social psychology, and anthropology. After eight years of building staff and program, he leaves behind a solid, functioning enterprise.

During this past year, the Laboratory has been most fortunate in recruiting Drs. William Caudill and Stanley Diamond. Dr. Caudill, now Chief of our Section on Social Studies in Therapeutic Settings, is widely known for his pioneering studies of the social organization of the mental hospital, as well as for his research on Japanese culture. Dr. Diamond brings to the Laboratory his wealth of anthropological field experience in Israel and Nigeria.

The departure of a Laboratory Chief is necessarily a time for stock-taking. We have now reached the stage in an organization's history where it is no longer necessary to be preoccupied with creating a new staff. We have a first-rate core staff in all three of the social sciences most relevant for an NIMH research program--sociology, social psychology, and anthropology. The state of the job market for the past two or three years has been such that we have not been able to attract as many people of the requisite quality in sociology as in anthropology and social psychology; we shall have to put special emphasis on seeking out sociologists. But, by and large, the growing stage is largely past, and we are now in a position to build on the people we have and the momentum they have developed.

In general, it may be said that the Laboratory as a whole is concerned with one major problem--the effects of social structure upon personality and behavior--with the Sections, and the individuals in those Sections, approaching the problem from a variety of vantage points. To some degree, the Section on Social Studies in Therapeutic Settings is marked by its interest in the structure and functioning of the mental hospital and by a cross-cultural orientation, the Section on Social Developmental and Family Studies by its interest in family relationships, and the Section on Community and Population Studies by its interest in how the organization of the larger society affects personality and behavior. But these are distinctions of emphasis.

Almost half of the current research in the Laboratory is focused on the family and personality development. Current studies range from broad-scale attempts to delineate variations in parent-child relationships associated with the family's social position, to more intensive studies of how particular aspects of parent-child interaction affect children's personality development. Considerable effort is being devoted to the twin problems of developing better concepts for interpreting family relationships and developing better methods for securing data. Methodological research on the use of observational data, on the validity of inferences based on retrospective reports, and on the consistency of reports given by various family members have been integrated into several of the substantive studies.

The concentration of attention on the family reflects its strategic importance for the personality development of the child. But the program includes, too, studies of personality in later years: research on the self-concept in adolescence, on the emotional reactions of men in their middle working-years to job stress, and on social aspects of gerontology.

During the past few years the Laboratory has developed an intensive program of research on the functioning of the mental hospital, a program now accounting for about one-third of our resources. Present studies include a comparison of Japanese to American mental hospitals, a large-scale survey of nurses' attitudes and behavior toward patients at Saint Elizabeths Hospital in Washington, D. C., participant-observational studies of the functioning of the mental hospital, and experimental studies with schizophrenic patients.

This represents a research program of considerable scope and diversity. It is a rich program, for it is made up of capable people pursuing the objects of their individual curiosities under the conditions of freedom essential to scientific accomplishment. But are we making the maximum use of the diversity of talents, interests, and points of view in the Laboratory? We probably have not done enough to establish the free marketplace for intellectual interchange that makes it possible for each investigator to benefit maximally from the presence of other people tackling similar problems in different ways. It should be possible to create working conditions so that as a group we accomplish far more than would be possible if each of us were working in isolation from the others. The challenge is especially exciting to social scientists, for the problems we face in the organization of our working-environment are the very problems with which our science deals.

The Section reports which follow present our program in greater detail.

Social Studies in Therapeutic Settings (CIB)

Dr. William A. Caudill

During the past year the members of the Section have been continuing their studies of therapeutic settings in the United States and in other cultures. Although many of our studies are carried out in therapeutic

settings as these are narrowly defined in terms of the hospital, the clinic, and the doctor's office, we have also interpreted our mission more broadly so as to include consideration of the therapeutic potential of such important social structures as the family, the school, and the peer group. A therapeutic setting such as a hospital exists, in one sense, only as a nexus of relations among staff and patients which, for members of both groups, is tied to other clusterings of significant relations in their past, their present, and their future. Although a hospital in one culture may appear superficially similar to a hospital in another culture, the manner in which these institutions, and the lives of those who work and live in them, are caught in the wider network of family and community organization may be remarkably different. This question is one of the reasons we have chosen to include a comparative cross-cultural dimension in our work.

During the year there have been two additions to the professional staff. In July, Dr. William Caudill, an anthropologist with research experience in American and Japanese psychiatric hospitals, joined the Section as Chief, coming from Harvard University where he had held the posts of Lecturer in the Department of Social Relations, Research Associate in the Department of Psychiatry, and Chief of the Department of Social Science at McLean Hospital. In October, Dr. Stanley Diamond, an anthropologist with field experience in an Israeli Kibbutz, an Arab village, and a primitive community in Nigeria, joined the professional staff of the Section, coming from Brandeis University where he had held the posts of Assistant Professor in the Graduate Department of Anthropology, and Research Anthropologist in the Department of Psychiatry at Massachusetts Memorial Hospital.

Through June of the past year the Section continued to be host to Mr. Yngvar Löchen, a sociologist and Visiting Scientist from the Dikemark Mental Hospital in Oslo, Norway. Mr. Löchen continued his comparison of certain aspects of organizational structure in Norwegian and American psychiatric hospitals. He was particularly interested in the relation between the formal and informal structures of the hospital as this relation affected the balance between considering the patient as a "case" and as a "person." The Section profited greatly from its contacts with Mr. Löchen, and we hope in the future to continue to provide opportunities for mutual exchange with visiting scientists from other countries.

Dr. Leonard I. Pearlin, a sociologist, in collaboration with Dr. Morris Rosenberg of the Section on Community and Population Studies, continued his studies at Saint Elizabeths Hospital in the search to identify therapeutically crucial attitudes among nursing personnel, to develop methods for their measurement, and to investigate the meaning of these attitudes in their interrelation with the differing social structure to be found in a series of wards in the hospital. The results of this study are described more fully below, and Dr. Pearlin plans in the future to make use of the methods and results of this study in a ten hospital cooperative study initiated by the Psychopharmacology Service Center. During the year, Dr. Pearlin also continued his work with several members of the Personality

Development Section of the Adult Psychiatry Branch on a study of how competent adolescents cope with the problems generated by transition from the senior year of high school to the freshman year of college.

Dr. Carmi Schooler, a social psychologist, continued a series of studies with schizophrenic patients. Dr. Schooler's basic interest is in the experimental study of the relationship between various psychological and social background factors and the regressed chronic schizophrenic's reluctance to affiliate with others. One experimental study in this area of interest was carried out during the past year at Springfield State Hospital, and the results are presently being analyzed. Another somewhat similar study is being planned which will investigate some possible factors in the chronic schizophrenic's attitudes toward social interaction by asking subjects to select the valued behavior patterns they prefer in individuals with whom they are expected to socialize. Dr. Schooler's interest along these lines has also led him to study the relationship between birth order and schizophrenia.

As is indicated by the range of academic disciplines represented in the Section, our studies have been carried forward using a variety of methods: anthropological field work, historical analysis, formal and informal interview techniques, surveys carried out through the use of schedules and questionnaires, and experimental designs. Some of the details of this work are indicated in the following descriptions of several of the projects being carried out in the Section.

Dr. Pearlin, in his study at Saint Elizabeths Hospital, devised and used two instruments. One was a structured questionnaire, completed by 1138 members of the nursing service. This questionnaire was designed to measure therapeutically relevant attitudes and also asked for material regarding the social and personal characteristics of each staff member. The second instrument, intended to gather information about characteristics of patient populations, programs, policies, and staffing patterns, was addressed to each of the 156 wards of the Hospital. With these data, it has been possible to examine a broad range of factors influencing attitudes relevant to patient care. One type of factor found to influence these attitudes concerns the social values of individual nursing personnel, many of these values being acquired as members of the larger community. Characteristics of wards to which personnel are assigned are also important determinants of attitudes. Most instrumental in attitude formation, however, are not staff or ward characteristics alone, but both of these together in certain combinations. One of the attitudes examined in this way is "status distance," defined as a withdrawal from patients by setting one's self above patients. Status distance is most likely to occur among staff assigned to wards containing patients of low social standing, but this is particularly true for personnel with the following characteristics: a relatively high position in the nursing order, an obeisant regard for authority, and blocked aspirations for occupational mobility. The importance of the interaction between individual and ward characteristics in shaping attitudes is also demonstrated in the case of "personal distance." Personal distance, defined as emotional

indifference to patients, is most frequently exhibited by staff working with patients whose ages are markedly different from their own. Nursing personnel working with patients of their own sex, however, express more personal distance than staff working with patients of the opposite sex. Thus, the study has isolated and explored a series of nurse-patient combinations that serve to reduce or expand psychological distance.

The first of Dr. Carmi Schooler's experimental studies with schizophrenics referred to earlier was based on a modification of a method for studying affiliative behavior developed by Dr. Stanley Schachter. In this modification each subject was brought to the experimental setting and told that she was going to be seen by a psychologist; the subject was then asked to wait because the psychologist was not yet ready for her. The subject was led into a waiting room containing two alcoves--an empty one, and one in which an assistant of the experimenter, dressed in the manner of a patient, was sitting. The subject was told she could wait in either alcove, and her choice of alcove as well as her reactions to the assistant served as measures of her desire for social affiliation. After four minutes of waiting, the subject was taken to a psychologist and given a battery of tests. Although the data from this experiment have not yet been fully analyzed, a preliminary analysis indicated that the chronic schizophrenics conformed to a pattern found by Schachter among normal subjects in which subjects born in earlier birth ranks were more likely to meet stress in a social manner than subjects born in later birth ranks.

The above finding led Dr. Schooler to study the relationship between birth order and schizophrenia. The method used for investigation consisted of an analysis of data from a 25 per cent sample of the schizophrenic female patients in Springfield State Hospital, and a re-analysis of data collected in other published and unpublished studies. As a result of this investigation, Dr. Schooler has found that: (1) In a sample of hospitalized female schizophrenics, significantly more patients came from the last half of their sibling group than from the first half. (2) In a sample of discharged patients there were disproportionately large numbers of last half catatonics and first half paranoids. From the data at hand, however, it cannot be concluded whether this finding can be true only for discharged patients since a similar, though not significant, trend exists among the hospitalized population. (3) In general, when the data from the various studies were combined, significantly more of the subjects were last born than first born. This difference, however, appears to be entirely due to the subjects from families of four or more. (4) It is impossible with the data at hand to separate the effect of birth order and maternal age. Because of this a follow-up study is now being planned to evaluate the relative effect of birth order and maternal age on schizophrenia.

Dr. Diamond, as indicated earlier, has done extensive anthropological field work, and he now plans to bring together Israeli, Arab, and Nigerian materials in a study of comparative socialization. He reasons that the Israeli Kibbutz represents a type of modern collectivism, and the Arab village represents a hierarchical and patriarchal society in transition to

more or less "Western" modes of behavior, and that the Anaguta of Nigeria represent a type of primitive, communally organized society. These three levels of organization--contemporary, transitional, and primitive--imply an over-all historical schema under which studies of socialization relative to the specific history and structure of each society can be subsumed. The objective of this inquiry, then, is to help broaden and develop the comparative-historical approach to those culturally determined aspects of the individual's life cycle. This inquiry may also provide us some keys in tracing the etiology and characteristic course of certain emotional disorders.

Dr. Caudill's current research is concerned with cultural and psychodynamic factors in the occurrence and treatment of psychiatric illnesses in Japan. Using mainly observation and interviewing, studies were made during 1958-59 of the organization and operation of three contrasting small Japanese psychiatric hospitals located in metropolitan Tokyo. In terms of treatment, the first hospital was organic in its emphasis, the second specialized in Morita psychotherapy, and the third utilized psychoanalytically oriented psychotherapy. In addition to these intensive observational studies, information was obtained on the history and present organization of psychiatry in Japan. A schedule calling for psychiatric and sociological information was constructed and completed for the approximately 600 patients who were admitted during 1958 to the three hospitals which were studied, and for an additional 200 patients who were admitted in 1958 to a large psychiatric hospital run by the city of Tokyo. A questionnaire asking for information on personal background and nursing career was administered to approximately 200 student nurses at two schools of nursing in Tokyo. A picture interview, using a series of eight pictures as visual questions, was devised and used with 80 subjects (divided among doctors, nurses, and patients) in the attempt to obtain data on what impulses were allowable or needed restraint in various life situations.

Specific findings are not yet available as analyses of the several parts of the data from Japan are still in progress, but it is hoped that this study will help determine the extent and nature of cultural influences on types of psychiatric illnesses and their treatment. On a descriptive level this involves identification of patterns of symptoms and preferred modes of care that are characteristic for a particular culture. On a more conceptual level this study should provide information on the effect of different cultural settings on the development of character structure and ego defenses. In line with this, the data should be of use in furthering understanding of the interplay between the human organism and its "average expectable environment" as this concept has been developed by Hartmann and carried further by Erikson. The reasoning in this regard is that both the patterning of the defensive structure of the personality and the nature of the "average expectable environment" are subject to cultural influences throughout the varying stages (or transitional crises) of the life cycle.

Social Developmental and Family Studies

Dr. Marian Radke Yarrow

The Section's primary research emphasis is on child development. The developmental areas in which the research falls can be summarized as three: (1) parental-child relationships, (2) developmental problems of a social psychological nature, and (3) problems of methodology in child development research. A secondary focus in the Section is on problems of human aging. The disciplines of social psychology and sociology are represented in the Section, bringing a wide range of theory and methodology to bear upon developmental problems. Interview and questionnaire techniques, field and laboratory experiments and controlled observations in natural settings of peer groups and family are being used.

In the search for critical variables in the socialization of the child, research in general stresses the mother-child unit, and in particular the mother's attitudes and practices of child-rearing. However, a mother rears her children within various family and cultural contexts which may directly or indirectly affect the mother-child relationship. It is with these contexts and their possible influences that several of the projects are concerned.

Investigations of the mother role in terms of the family's social class, racial membership, and the mother's employment status are being carried out in two related studies. Mr. Gillette has been interested in how differing combinations of class, race, and employment statuses operate to influence (1) the nature of husband and wife participation in family functioning and (2) the mother's concept of herself and her satisfactions in her various roles. Questionnaire data were obtained from 700 mothers from different social class levels in Negro and white groups in the Greater Washington area. The degree and types of father and mother participation in various family tasks and the degree of consensus between husband and wife on family norms are shown to differ significantly by class and race. Middle-class fathers are more likely than working-class fathers to share in household tasks. Fewer discrepancies between husbands and wives in attitudes toward family issues are reported by middle-class than by working-class mothers. These class differences are accentuated by controlling for maternal employment status, with greater participation by the husband and greater husband-wife consensus in families in which the mother is employed. Mothers' concepts of themselves and their satisfactions from mother, wife and career roles also differ by class and race. Employment is less likely to be seen as incompatible with the mother role by Negro women than by white women, regardless of class.

Dr. Yarrow has used a subsample from the preceding study to investigate associations between mother's employment and child rearing practices. The combination of mother role and work or career role introduces a number of changes into the family. It may introduce a factor of maternal separation or multiple-mothering in the upbringing of the child. It might also be

hypothesized that specific rearing philosophies and practices would be associated with the maintenance of a work role by the mother. Of particular interest are mothers' child rearing practices with regard to independency training, permissiveness of aggression, achievement motivation, and sex role typing. At present, only preliminary analyses have been completed. They indicate very slight differences between employed and non-employed mothers in child rearing philosophies and practices, when class and race are controlled.

The unique position of each child in his family group, in terms of his sex role and sibling order, is being studied as another context within which the mother-child relationship develops. Dr. Campbell and Dr. Yarrow are beginning studies in this area. The basic research tool of these studies is the interview.

Drawing upon various cross-cultural studies of primitive societies, Dr. Burton has analyzed a number of structural characteristics of families, with an interest in the formulation of a theory of identification which would integrate findings from varied cultural sources. He has shown in this analysis that the absence of the father or the exclusive mother-son relationship in infancy and early childhood is associated with certain developments and customs during adolescence. These associations in primitive cultures appear similar to associations found between the family structures of certain lower class subgroups within our society and the incidence of delinquent behaviors in adolescence in these groups.

As indicated earlier, a number of studies in the Section share a common focus upon social psychological development of children. A study of children's cognitive processes in social experiences--their appraisal of other persons, their sensitivities to and interpretations of interpersonal relations--has been completed by Dr. Campbell and Dr. Yarrow. Two hundred sixty-seven children between eight and thirteen years of age were interviewed and observed in resident camp settings. Sensitivity in social perceptions--measured by the child's ability to give complex descriptions of others and to integrate diverse characteristics of the other person into an organized impression, often including inferences regarding the motives underlying observed behavior--shows an increase with the age of the children. Cognitive complexity is also associated with a child's adjustment to his group. High status among peers is associated with higher scores on the several measures of cognitive complexity. Children showing a high frequency of interaction in the peer group, as contrasted with a withdrawn pattern, tend to have the higher ratings in quality of social perceptions. Boys and girls do not differ in these respects, but they tend to emphasize different features in their reports on the characteristics of others; boys report more on aggressive features of interaction, girls on nurturant aspects.

Dr. Burton has underway a series of experimental studies on the processes of internalization of rules, standards and values, with special emphasis on resistance to temptation and guilt. What are the conditions which dispose young children to conform to established rules or to yield to

the temptation to break rules? Further, what are the psychological after-effects of resistance or yielding? What are some of the child-rearing antecedents to variations in children's internalization of moral standards? Measures of conformity to established standards are obtained in experimentally controlled test situations. Psychological effects of the temptation effect are measured through the use of incomplete-story techniques. Observations of mother-child interactions in controlled situations furnish data on child-rearing variables.

A number of projects in the Section have methodological interests as their focus. As a methodological by-product of the study of children's social perceptions, a study of intermeasure correspondence in the appraisal of social relations has been undertaken. Three different sources of data--children's ratings of one another, adults' ratings, and observational records of interaction--provided data from which to compare various measures on the children. A wide variation in degree of intermeasure correspondence appears: For some variables, such as popularity status, a considerable degree of intermeasure agreement is obtained. For others, such as appraisal of anxiety, considerable intermeasure discrepancy exists.

A major methodological study is the investigation by Yarrow and Campbell of the nature of mothers' retrospective reporting on events and conditions pertaining to the earlier development of their children. The technique of recall has considerable prominence among the techniques of research used in investigating the significance of childhood experiences for later development. Most often the parent is asked to reconstruct his precepts and practices in caring for his child or to describe the characteristics of his child at some designated earlier date. The aims of the study are to assess the nature of differences between earlier events and parents' recollections of such events, and to determine how retrospection is influenced by such factors as time interval, intervening events, and present psychological situation. The data collection on 250 families is very nearly completed and some analyses have begun.

In the area of human aging, Dr. Yarrow has collaborated in the NIMH interdisciplinary study of healthy aged men and, with the interlaboratory group, is now completing a book on the Biological and Behavioral Aspects of Human Aging. This investigation brings the perspectives and measurements of of physiology, psychiatry, psychology and sociology to the examination of factors in human aging. The social psychological interests lie in (a) analyses of the psychological environments of the aged, (b) the attitudes and behavior of the aged in their present life circumstances, and (c) relationships between these factors and the data from physiology, cognitive functioning and psychiatric assessments. Significant relationships have been found between environmental losses suffered by the elderly, particularly losses in love-objects, and many aspects of their daily functioning and adaptive capacities. The individual's social adequacy, measured by the complexity of his daily behavior and his maintenance of goals and social relationships, shows significant relationships to laboratory measures of cognitive functioning, reaction time, cerebral metabolism, the subject's own evaluations of age declines, and depressive symptoms.

A follow-up study is just now beginning of the men who were studied intensively four years ago. The objectives of the follow-up are to examine stabilities and changes that have occurred with time and to determine the predictive value of certain physical and psychological indicators present four years ago for current status and functioning.

Community and Population Studies

Dr. Melvin L. Kohn

The three studies being conducted in this Section, quite disparate in focus, share a common concern with the impact of the organization of the larger society upon personality and behavior. In the first study, Dr. Stephen Boggs is concerned with the ways in which one's work career affects one's values and one's emotions. The second deals with adolescents, rather than adults: it is an exploratory study, conducted by Dr. Morris Rosenberg, of the social determinants and consequences of adolescents' self-conceptions. In the third, Dr. Melvin Kohn, Dr. John Clausen, and Miss Eleanor Carroll have been examining the effect of social class upon parents' values and practices.

The first of these studies is based upon a survey that Dr. Boggs conducted among the research technicians and assistants in the various laboratories of the NIH. He concentrated on men in the age group where the realities of limited further advancement become inescapable. Thus far in his analysis he has dealt principally with what happens to men's values in the course of their careers. One pregnant finding is that as men hit the promotion ceiling, they become preoccupied with advancement, rather than intrinsic job interest or even security. Men farther along in their careers, frustrated in their desires for promotion, are even more likely to be advancement-oriented than are the younger men who have not yet come face-to-face with limited opportunity.

Dr. Rosenberg's study of adolescents' self-conceptions is based on a questionnaire he has administered to a representative sample of 5,077 high school students in the State of New York. The questionnaire is broad-gauge: it attempts to secure information about these adolescents' self-evaluations and their ideals, about those personal and familial experiences that may be relevant to their self-conceptions, and about those aspects of their behavior that would presumably be most directly influenced by their self-conceptions. The data are in hand and the analysis underway, but it is too early to report results. One unusual aspect of this research might be noted, however. While there has been much informed speculation about the social determinants of self-conception, the research that has been done on this problem has taken little account of the multifaceted nature of self-conceptions or of the complexity of inter-related variables with which any study in this area should deal. Dr. Rosenberg, by using a questionnaire rather than more intensive interviews, has chosen to sacrifice the opportunity for securing a great deal of information about each of his respondents in

favor of having at his disposal sufficient information about a large number of individuals to be able to do the complex multi-variate analysis the problem demands.

The work done this past year on the study of social class and family relationships represents the culmination of a long-term study; it may thus be useful to review not just this year's work, but the project as an entity. (The study is based on interviews with mothers in a representative sample of 339 Washington, D. C. families, plus independent interviews with fathers and children in one-fourth of those families.)

Rejecting the oversimplications that working-class parents differ from middle-class parents principally in a greater propensity to use physical punishment and a readiness to permit their children a greater range of freedom, the investigators approached the problem by attempting to understand the ideologies of parents in both social classes and then tracing out the behavioral consequences of these ideologies. The study has shown decidedly different emphases in middle- and working-class parents' values for their children. The dominant motif of middle-class parents' values is that the child develop his own standards of conduct: desirable behavior consists essentially in the child's acting according to the dictates of his own principles. By contrast, the dominant motif of working-class parents' values is that the child's actions be reputable: desirable behavior consists essentially in his not transgressing parental proscriptions.

Both middle- and working-class parents use physical punishment--when milder methods of discipline do not work. Further, parents of one class use physical punishment about as frequently as do parents of the other. But they resort to the hand and rod under quite different circumstances. Faced with the problem of whether or not to punish a child's misbehavior, middle-class parents look to the child's motives and feelings. Working-class parents look, instead, to the act itself; their attention is focused on the direct consequences of misbehavior. The middle-class child is more apt to be punished for loss of self-control, the working-class child for disobedience.

Having seen the implications of parents' values for their disciplinary practices, the authors considered what the effects on the overall structure of family relationships might be. They assumed that inherent in parents' standards for their children must be conceptions of their own responsibilities as parents. Specifically, it seemed that middle-class values imply a parental obligation to be sensitive to the child's thoughts and feelings; working-class values imply a parental obligation to make clear to the child what rules are to be obeyed. One consequence should be for the ratio of support to constraint in parents' handling of their children to be higher in middle- than in working-class families. Another consequence should be for mothers and fathers to divide the responsibilities for the support and constraint of the children differently in the two social classes. In particular, given their own and their wives' ideologies, middle-class fathers should be expected to play a much larger part in providing support to the children than do working-class fathers. It would seem more appropriate to working-class ideology that the father's role center on the imposition of constraints.

Both expectations are borne out by the data. This has important theoretical implications above and beyond an interest in the impact of social class on family relationships. Most theories of personality development have been based on the model of a family in which mother's and father's intra-familial roles are necessarily differentiated, with mother specializing in providing emotional support and father in imposing constraint. However useful a first approximation this may be, both middle- and working-class variations on this general theme are sufficiently great to compel a more precise formulation.

The data are at least partly consistent with the mother-supportive, father-constraining formulation, for even in middle-class families almost no one believes that the child turns to father more readily than to mother. Yet, in a sizeable proportion of middle-class families it is mother who takes primary responsibility for imposing constraints on sons, and father is at least as supportive as mother. And although middle-class fathers seldom seem to be as supportive of daughters as are their wives, it cannot be said that fathers typically specialize in constraint even with daughters. In most middle-class families, mother's and father's roles do not seem to be sharply differentiated. To the degree that they are, a new division of responsibilities is developing, with each parent taking special responsibility for support of children of his own sex.

Mother's and father's roles are more sharply differentiated in working-class families, with the children almost always feeling that mother is the more supportive parent. Yet, despite the high valuation put on the constraining function, fathers do not necessarily specialize in setting limits for the children, even for the sons. In some working-class families mother specializes in support, father in constraint; in others--perhaps in most--the division of responsibilities is that mother raises the children, father provides the wherewithal. This pattern of role-allocation probably is and has been far more prevalent in American society than the formal theories of personality development have recognized.

Office of the Chief

Dr. Melvin L. Kohn

Dr. Gordon Allen (the sole geneticist in a social science laboratory) has devoted himself to two principal projects. The first is an assessment of factors in mental deficiency, based on a reporting system set up in 1937 by Dr. Allen's collaborator, Dr. Franz Kallmann, which provides index information on a large number of mentally subnormal twins in New York State. Dr. Allen studied many of these twins, 178 pairs in detail, classifying them as to zygosity, and obtained relative concordance rates for two major diagnostic classes. In the more severe types of mental defect, with evident congenital or neonatal pathology, he found a clear contrast between monozygotic and dizygotic twins. This he interprets as evidence that genetic factors play an important role, interacting with nongenetic factors that may also be elucidated by further analysis of the data.

Dr. Allen's other study is more methodological in intent; he is trying to develop better techniques for the determination of zygosity in triplets and quadruplets as well as in twins. For a set of twins there are only two possible hypotheses about zygotic origin. For triplets there are five and for quadruplets, fifteen. Some of the triplet and quadruplet hypotheses cannot be differentiated on the basis of simple genetic traits like blood groups, and quantitative differences must be brought into the calculations. This can apparently be done by combination of individual probabilities for separate pair differences within the set. A likely formula has been found for combining the probabilities, but it still lacks theoretical and empirical validation.

Dr. Melvin Ember has formulated a study of authority in the mental hospital. In this study, he will use anthropological field methods similar to those he developed in research on the legitimacy of authority in American Samoa. He plans to study three large nursing units selected as manifesting differences in the degree to which nursing staff accept as legitimate the formal authority structure. Intensive observation and interviewing will be conducted in one of these units, for the purpose of developing quantifiable measures of the amount of authority accorded by each member of the unit to the others. The indices developed on that nursing unit will then be used on the others. The rationale here is to use the phenomenological approach of the anthropologist who goes into a new field with a formulation of objectives and overall research design, but develops the niceties of design and the specific indices out of the material the culture presents to him--in this instance, the "culture" being the mental hospital.

National Institute of Mental Health
Research Grants and Fellowships Branch

Annual Report for Calendar Year 1960

I. PROGRAM GROWTH AND DEVELOPMENT

In the thirteen years since the establishment of the Institute's grant program, mental health research has moved forward slowly but steadily in the many fields comprising its totality. As could be expected because of its complexity, relatively few advances toward any conclusive understanding of the multi-factored etiology of mental and emotional illness were made in 1960. Important advances have been made in the field of mental retardation, as discussed below. Progress in treatment methods and in the application of mental health principles to problems of special social concern were also noteworthy. Contributions to basic research, for the most part immeasurable for years to come, continued to accumulate. Throughout 1960 the Research Grants and Fellowships Branch extended its effort to provide those types of grant support and consultative services, predicated upon an expanding knowledge of the needs of the field, which could most adequately anticipate, and help to meet, the needs of research investigators throughout the country.

The deep national commitment to research as a core approach to problems of mental illness was again affirmed in f.y. 1960 Congressional appropriations for research grants. In f.y. 1959 the over-all appropriation for all types of research grants was $18,834,000; in f.y. 1960 it was $23,482,000. The f.y. 1961 appropriation (available during the second half of calendar year 1960 and the first half of f.y. 1961) totals $34,235,000.

During calendar year 1960, 1,238 mental health research grant applications, (exclusive of mental health project and special grant applications) were reviewed, as compared to 1,195 in 1959, 822 in 1958, 683 in 1957, 457 in 1956, and 260 in 1955. Of those 1,238 applications reviewed in 1960, 641 were recommended for approval, about 51 per cent as contrasted with a 49 per cent approval rate in 1959.* Including both new and continuation applications a grand total of 1,062 grants was supported during f.y. 1960. The mean amount awarded in each research grant during f.y. 1960 was $21,463, as contrasted with $20,921 in f.y. 1959, $19,960 in f.y. 1958, and $16,651 in f.y. 1957.**

*Review and approval figures cited here refer to applications received in time for consideration during the annual year by the National Advisory Mental Health Council. They include all "regular" research, psychopharmacology, career investigator, and small grant applications. They cover new applications, requests for supplements, and requests for continuation beyond commitment. Annual requests for continuation within commitment, which are not brought before the Council, are excluded.

**These and subsequent statistics on the research grant program include all types of NIMH research grants, which are coded in the RG&F Branch grant classification and analysis program.

The program continues to be characterized by a wide variety of research disciplines and fields of knowledge. Of those 2,113 research investigators on all grant applications supported during f.y. 1960, for example, 33 per cent were psychologists, 17 per cent psychiatrists, 12 per cent in "other clinical medical fields," 18 per cent in the biological and basic medical sciences (such as physiology, experimental neurology, genetics, etc.) and 9 per cent in the social sciences. An analysis of the grant support in f.y. 1960 by primary field of study, showed 47 per cent ($10,847,065) in psychology; 19 per cent ($4,274,010) in psychiatry; 11 per cent ($2,447,031) in the biological and basic medical sciences; 6 per cent ($1,456,157) in the social sciences; 2 per cent ($446,774) in "other clinical medicine," plus 34 per cent in a variety of other areas ranging from nursing to statistics, including a considerable number of interdisciplinary projects encompassing more than one field of study.

Of those research areas of special programmatic interest to NIMH, schizophrenia commanded the heaviest investment, commensurate with its position as the most prevalent of the major mental illnesses in the United States. Following is a comparative table of annual awards in selected program areas during f.y. 1960:

Table I

Program Area	No. of Grants	Dollar Amount (%)
Schizophrenia	232	$6,645,761 (29%)
Psychopharmacology	233	5,722,585 (25%)
Mental retardation	76	1,818,361 (8%)
Juvenile delinquency	47	1,357,760 (6%)
Alcoholism	42	1,087,574 (5%)
Aging	33	1,071,778 (5%)
Drug addiction	21	433,302 (2%)

Program Administration

While the day-to-day workload of administering a multi-million dollar grants program continued to place exceptional demands on the present staff during 1960, a significant increase in the degree of integration and improvement of procedures was obtained.

The appointment of a social psychologist to assist with program administration and consultative service with grantees helped in meeting some of the heavy Branch responsibilities in this area. New appointments of junior professional staff in the grant classification and analysis program helped to consolidate and improve the activities of this unit. Towards the end of the year, an additional medical research program specialist, with responsibilities in reporting the results of the grant program, was added to the staff. Additional professional and clerical staff are being recruited for duties in the very sizable task of identifying and reporting the results of the multi-disciplinary mental health research grant program. To assist in the provision of personnel and other administrative services for the Branch, which presently

numbers 62 persons, an Assistant to the Administrative Officer was also appointed during 1960. Additional staff was also added in the Psychopharmacology Service Center.

Further appointments in Branch program development, program administration, program analysis and reporting activities are essential if the present staff is to maintain and strengthen its performance level in all areas. While recruitment is actively underway for these positions, the crucial shortage of space has severely hampered such operational planning. Program activities will continue to be impeded unless further provision of space is given early consideration. This problem is NIH-wide, of course, and directly related to the markedly increased program responsibilities which have been placed on NIH staff by the substantial Congressional directives and appropriations of the last five years. The aim and purpose of the NIMH grant program, however, will continue to be seriously obstructed if the functional efficiency of the research grants staff continues to be blocked by shortage of space.

Program Analysis Activities

The Grant Classification System. During 1960 a revised coding and classification system for all types of NIMH research grants was initiated, focusing on the subject matter and administration of the program. The major categories of information for which data are being collected include the scientific fields of study involved, the disciplines and training of all investigators, the types of institutions in which investigators are working, the support given by institutions other than those directly sponsoring the research, the disorders and symptoms studied, the clinical goals of the research, the data-gathering techniques utilized, the types of subjects studied, the research approach (clinical versus experimental), the research emphasis (applied versus basic), the strengths and weaknesses of the research as judged by study sections and Council, and the major social, psychological, and biological variables studied.

Program analysis staff completed the coding of material for the research grant programs supported in fiscal years 1956 through 1960. Entry of the coded data for fiscal years 1959 and 1960 on punch cards was completed, and analyses were carried out for presentation to the National Advisory Mental Health Council and for subsequent publication.

In the light of these analyses, revisions were made in certain aspects of the coding and classification system in order more effectively to meet the needs of the Branch for information retrieval and program description; coding of materials for the f.y. 1961 program was also begun. Beginning with f.y. 1961, all disapproved applications will be coded routinely, thus adding another valuable dimension to the analyses.

During the year, the coded research information has served the Branch in its continuing responsibility to provide pertinent data about the program upon request. It has been possible, for example, to prepare machine-printed lists of grants for the entire program supported within a given fiscal year (including grant number, type, short title, investigator, amount of award,

institution, and location), and specific lists of research in such diverse areas as hypnosis, nursing education, social behavior among animals, sensory deprivation, depression, speech disorders, psychosomatic factors in children's asthma, suicide, social interaction in hospital wards, research underway in specific States, and many others. Such lists have been prepared at the request of a variety of sources, among them scientists in the field, Branch and Institute staff, other federal agencies, professional societies, and representatives of mass media. A special list of all research in the social sciences was prepared and made available at the American Sociological Association meetings in New York in order to acquaint interested investigators with the scope of the program. A number of analytic papers and memoranda based on coded program analysis data were also prepared during the year, including a review of NIMH research in the social and behavioral sciences, and another analyzing information about current coding and classification systems in bio-medical research.

Analysis of the Research Grant Program, 1948-1960. During 1960 a substantial analysis of fiscal information and data relating to major program areas was prepared and presented to the National Advisory Mental Health Council.* Following are some of the major findings:

1. The range of grant award amounts has expanded steadily since the beginning of the program
   a. In 1948 the largest annual award was for $26,500; in 1960 it was for $230,000.
   b. In 1950 over half of the annual grants awarded by NIMH were under $10,000; since 1958, grants under $10,000 have accounted for only about one third of the total effort, despite the initiation of the small grant program in 1956.
   c. In 1954 only 2 per cent of the grants were for amounts over $50,000; in 1960 there were 10 per cent in that category.

2. The total number of grants awarded in 1960 was over one third as large as the total number awarded in all previous years; the comparable proportion for amount of awards was 43 per cent.

3. Amounts awarded for continuation grants have been higher than for new grants.
   a. Of all the grants awarded between 1948 and 1960, roughly half were continuations and half were new; however, 61 per cent of the total amount awarded during that period was for continuation grants as against 39 per cent for new. Even when small grants (all of them new and all for small amounts) are removed, the ratios of continuation-to-new are still in the same direction.
   b. The mean continuation grant has been consistently larger than the mean new grant. Excluding all small grants,

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*Julius Segal, "A Summary of the Research Grant Program of the National Institute of Mental Health: 1948-1960" (November, 1960).

these differences range from $1,272 in 1958 to $9,797 in 1950; the grand mean continuation grant (1948-1960) was over $8,000 greater than the grand mean for new grants.

4. The mean annual award for all NIMH grants has more than doubled between 1948 and 1960; the median award has increased by 80 per cent. Since 1957, the first year of considerable activity in the small grant program, the modal grant has remained at a constant (under $2,500) level.

5. The growth of the NIMH grant program has been attended by a diversification of effort reflected in the growing variety of distinct grant programs differing in their size, scope, and purpose.

6. The proportion of the total annual effort in selected, major program areas has risen steadily over the years - from 29 per cent in 1948 to 53 per cent in 1960 in terms of number of awards, and from 34 per cent to 63 per cent in terms of amount awarded. These include aging, alcoholism, drug addiction, juvenile delinquency, mental retardation, psychopharmacology, and schizophrenia, and represent areas for which Congress has specifically earmarked funds, or in which it has asked that the Institute devote special effort.

7. The grand mean amount of award for research in all selected program areas but drug addiction is higher than the grand mean for the over-all program. This would indicate that NIMH has been responsive to public health needs as reflected by Congressional action.

The compilation of the thirteen-year fiscal history of the program has provided a valuable tool for current program evaluation as well as for future planning. The variety of data prepared through the grant classification system may also serve as one basis for later evaluations of the program in terms of substantive accomplishments.

Survey on Private Support for Mental Health. To increase staff knowledge of the needs of the field and the services available to assist in meeting such needs, the Branch two years ago initiated a national survey of support which might be available from private organizations for research, training, and service activities in mental health and related disciplines.* The survey, which included almost 1,200 foundations and other national grant-awarding agencies, was completed during 1960, was presented to the National Advisory Mental Health Council and will be published through the Government Printing Office.

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*Jeanne L. Brand, "Private Support for Mental Health and Related Disciplines," (November, 1960).

Among some of the findings of the survey are the following:

1. Apart from the over-all area of "mental Health or mental illness per se," the most popular fields of support in areas of interest to mental health are psychiatry, juvenile delinquency, the biological, physiological, and biochemical aspects of mental illness and child development and behavior.

2. Support by private organizations for all types of mental health activities on a national level is currently estimated roughly at $14,500,000 annually; research grant support at $3,600,000.

3. Of those types of support being made available in private giving, research and service were offered most frequently. Less adequate private support exists for construction or building as well as for travel needs of professional personnel working in mental health fields.

The report also discussed at some length the methods of operating of foundations supporting this field and provides detailed information on the assets of participating national organizations and their respective interests in mental health disciplines. Early reactions of foundation executives and Public Health Service staff reviewing the survey indicate that it may prove to be a useful reference tool for research investigators and others working throughout the country in the field of mental health.

Program Resource and Development Activities

Throughout the year the 28 professional members of the Branch staff continued and expanded their services to grantees and to mental health research through consultations at scientific meetings, presentation of professional papers, participation in symposia, study panels, work-groups and forums, as well as in a variety of consultative and evaluatory visits to medical schools, university departments, state hospitals, clinics, etc.

The multidisciplinary nature of the program is emphasized by the wide range of professional meetings to which Branch staff contributed. Among the large, national professional societies at which papers were presented and discussions with current and potential grantees carried out were the American Psychiatric Association, The Federation of American Societies for Experimental Biology, the American Psychological Association, American Public Health Association, American Psychoanalytic Association, American Psychosomatic Society, American Chemical Society, American Society for Pharmacology and Experimental Therapeutics, American Pharmaceutical Association, American Association for the History of Medicine, Society for Biological Psychiatry, American Sociological Society, and the Group for the Advancement of Psychiatry. Regional meetings, like those of the Eastern Psychological Association, Eastern Sociological Society, Western Psychological Association, Midwestern Psychological Association, also provided opportunities to discuss the resources and requirements of the program with respective grantees.

Although federal grant programs have now been in operation for a number of years, the staff has found that many research investigators, faculty members, and graduate students are unfamiliar with the resources of federal grant programs. Late in 1959 a review and analysis of the grant programs of the Department of Health, Education, and Welfare was prepared for presentation at a conference on mental health research held in Indiana.* Since that time many requests for this publication have been received from universities and professional groups throughout the country, indicating the continuing need for provision of such information on program resources. Wherever possible Branch staff visiting medical schools and university departments attempt to provide better understanding of the various grant programs of the National Institutes of Health.

Branch staff also served as participants and consultants in such major national and international meetings as the White House Conference on Children and Youth, the International Congress of Psychology, the Collegium Internationale Neuro-Psychopharmacologicum, Pan American Medical Association, the National Health Council's 1960 Forum on the Positive Health of Older People, and the World Federation for Mental Health. Commensurate with the active research collaboration and program stimulation carried out at the direct command of Congress by the Psychopharmacology Service Center, PSC staff during 1960 extended their informational and advisory services through participation in special symposia on the use of psychopharmacologic agents, regional conferences on drug evaluation and community care, and special conferences on drug therapy.

Long-Term Programmatic Support

In 1960 seven more outstanding research investigators were recommended for and/or awarded seven-year program grants, thus bringing to a total of ten the number of those investigators chosen for such support. Research investigators selected for these long-term awards are mature persons of unusually high merit and competence in their respective fields, persons of proven productivity. Long-term program grants guarantee to the investigator a maximum of freedom, stability of support and flexibility in carrying out broad-range investigations. Such awards facilitate his planning and may contribute to the development and integration of skilled research teams.

Program grants of this nature currently range annually from a low of $22,813 per year to a high of $153,000, and average roughly $62,500 each. The fields in which these awards have been made have primarily been in the areas of physiological and experimental psychology, with one grant in clinical psychiatry and one in biochemistry.

In addition to the seven-year awards, a growing number of five and six-year grants are also being provided.

Research Grant-Supported Conferences

During 1960 the Institute awarded a number of grants to support confer-

*Philip Sapir, "Research and Training Assistance Available from the Department of Health, Education, and Welfare," November, 1959.

ences. Some, like the Soviet-American Joint Conference on Pavlovianism which was sponsored by the New York Academy of Sciences, had as their primary purpose the exchange of scientific information within a specialized area of research. A grant to the University of California for a conference on computer techniques provided an opportunity for needed assessment of the role of computer services in various areas of research. An award to the American Psychological Association to hold a second conference on research in psychotherapy gives promise of another valuable meeting, like its 1958 predecessor, for a continuing review and assessment of findings in a difficult research area.*

The importance of providing funds to bring together, on both a national and international level, outstanding scientists in specialized areas of research is underscored by the difficulty experienced by many investigators in obtaining any private funds for such purpose. Among the international conferences for which awards were given in 1960 were the Fourth International Neurochemical Symposium, the International Congress of Psychology, and the forthcoming Third World Congress of Psychiatry.

International Health Activities

During 1960 the Institute, concomitant with the strong Congressional support for extending U. S. cooperation in international health activities, increased its participation in the international aspects of mental health research in a variety of ways.

Grant support for a number of international research conferences has already been noted. Five hundred thousand dollars of the NIMH research grant appropriation for f.y. 1961 was allocated to the central NIH fund for support of international health programs. Whereas in f.y. 1959, 14 foreign awards for a total of $172,129 were made in the NIMH research grant program, 22 grants, totaling $289,249 were awarded in f.y. 1960.

The 1960 foreign grants were given to research investigators of exceptional competence, in accordance with the Public Health Service requirement that the research be of such nature that it can best be conducted outside the United States and that support is indicated in anticipation of findings of general importance to medical research. Foreign research grants, which were awarded to investigators in nine countries, support studies in psychophysiology, neuroanatomy, child psychology, social psychology, psychopharmacology, biochemistry, ethology, and other research areas.

In addition to assisting foreign research through the research grant program, the Institute also supported 37 research fellows from the U. S. in 28 foreign institutions during f.y. 1960. Grant support for cross-cultural studies of many areas of mental health research also increased during f.y. 1960, with investigations on such varied topics as cross-cultural studies of psychopathology, of geriatric stress, of infant development, and of the compar-

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*E. Rubenstein, M. Parloff, eds., Research in Psychotherapy, Proceedings of a Conference, Washington, D. C., April 9-12, 1958, Washington D. C.: National Publishing Co., 1959.

ative use of alcohol among different national groups.

As the Congress emphasized in 1960, disease knows no national boundaries. In many areas of mental health research continuing liaison and interchange with foreign colleagues is helpful in the development of American research. The extension of NIMH support to foreign scientists through the research grants and fellowships program is also a further token of U. S. active international good will.

The Small Grant Program

The small grant program, after more than four years, is a well established part of the Institute's research grant program. A total of 490 small grants have been awarded since May 1946 when the program began.

From October 1959 to November 1960, the Mental Health Small Grant Committee reviewed a total of 269 applications. It recommended approval of 132 applications and disapproval of 137 applications -- an over-all approval rate of 49 per cent. A total of $286,849 in small grants was recommended for approval for the period of these six meetings. Although this amount represents less than 1 per cent of the total NIMH research grant program, in terms of number small grants comprise 14 per cent of the total. Small grant applications continue in the majority (70 per cent) of cases to represent the investigator's first attempt to obtain Public Health Service support. Thirty-six per cent of small grantees, to date, have applied subsequently for regular research grants, with an approval rate of 63 per cent as compared with an over-all approval rate of approximately 33 per cent for new applications and for regular grants.

During calendar year 1960 the Committee and staff gave considerable thought to ways in which the program might better fulfill its original aims of providing rapid and flexible support to promising young investigators, to institutions with little previous engagement in research, and for exploratory and pilot investigations. With these aims in mind the Committee made several recommendations.

The Committee again recommended that the maximum small grant be raised from $2,000 to $3,500 for direct costs, plus 15 per cent for indirect costs. This recommendation was endorsed by the National Advisory Mental Health Council in March 1959, but has not yet been implemented. A number of factors had led the Committee to make this recommendation. For example, after necessary clerical help or salary supplement is included in the budget of a small grant, little or nothing is left for necessary equipment and supplies. The majority of applicants, therefore, request either salary or equipment. Salaries for graduate assistants are at least $2,000 a year in most institutions, and faculty summer salaries, even for assistant professors, usually amount to more than $2,000. In addition, very few anthropological field trips or sociological field studies can be made for less than $3,000.

The Committee members also decided to consider any and all existing research-related needs for support in the mental health field which might occur to them from the vantage point of their professional positions, and then to

determine whether these would fall within the scope of the small grant program or whether they might be more appropriate to other National Institutes of Health programs. After an extensive discussion the Committee made several recommendations, some specific to the small grant program and others more appropriate for consideration by other NIH programs of support.

The Committee felt that following the aims of the original program, greater attention should be given to encouraging the use of small grants to provide emergency funds or support for the "need money quick" request from established investigators, without requiring justification in detail. The Committee also felt that the small grant program should be receptive to applications from retired scientists, who are often in need not only of research support, but also of publication funds or salary to enable them to write up the results of completed research. Among the Committee's recommendations for other programs were the provision, through the fellowships program, of supplementary costs for dissertation research and part-time or short-term fellowship support.

The Committee's reaffirmation of earlier program goals and other recommendations are presently under consideration by the National Advisory Mental Health Council and the National Institutes of Health.

II. THE SUBSTANCE OF THE MENTAL HEALTH RESEARCH GRANT PROGRAM

The mental health research grant program in 1960 demonstrated the use of numerous scientific avenues of approach to the study of mental disorders. Although each branch of science evolves its own philosophy and its own patterns of discovery, the findings in any one branch tend to increase knowledge in the others. Knowledge of the factors involved in the etiology and treatment of mental disorders is derived from all the sciences concerning man in relation to his environment. The Institute, therefore, has continued to support research in scientific areas ranging from biochemistry and neurophysiology to psychology, sociology and anthropology. It is hoped that this research will lead to an understanding of the basic biological and psychological functions and dysfunctions of man, of normal and abnormal growth and development, and of those factors in the social context within which man lives and acts from the time of conception to old age. Included among the research areas of special social significance are mental retardation, schizophrenia, juvenile delinquency, alcoholism, drug addiction, and problems of aging.

The following distribution of the 1062 grants supported in fiscal year 1960 provides an estimate of the relative concentration of effort in those research areas by which the etiology, diagnosis, treatment and prevention of mental disorders will in time be understood.

TABLE II

Distribution of Number and Amount of Grant Awards by Research Area

Over-All Research Areas	Estimated No. of Individual Research Projects in Area	Estimated Amount Expended in Area
Biochemistry of Mental Illness	90	$ 1,381,488
Brain Mechanisms and Behavior	89	1,874,576
Pharmacotherapy in Mental Illness	135	3,254,074
Addiction to Alcohol and Drugs	46	1,061,987
Diagnosis and Treatment in Mental Illness	178	3,299,608
Basic Thought Processes	86	725,432
Problems of Aging	28	966,311
Mental Disturbances in Childhood	188	4,715,645
Social Factors in Mental Illness	86	1,429,493
Improved Care and Rehabilitation of the Mentally Ill	130	3,998,505
Scientific Evaluation Grants	6	87,060
Estimated Total Grant Support f.y. 1960	1,062	$ 22,794,179

It is impossible annually to review in detail the results of grant-supported research in all areas of the program. The Branch each year provides a comprehensive survey of research in one or two areas, with more limited illustrative discussion of other areas of the program. Last year research in schizophrenia was reviewed at some length. This year developments in the field of mental retardation are of special note.

Mental Retardation

It is estimated that there are some 5,000,000 persons in the United States who are mentally retarded. Since all members of the patient's family are, to some degree, disordered by the patient's illness and assuming that each patient is a member of a family of four, it can be seen that some 20,000,000 persons in the United States today suffer from the impact of mental retardation. The magnitude of the problem is well recognized as demonstrated by the intensified research for the etiological factors in this disorder. In 1960, 76 grants were awarded and approximately $2,000,000 expended for the study of mental retardation. In addition, a large number of grants in ancillary sciences, which are basic to all studies in mental health, contribute a large share of information to our understanding of mental retardation.

Biological Basis of Mental Retardation. In the past year studies concerned with the etiology of mental retardation tended to emphasize those factors which produce anatomical or chemical abnormalities of the nervous system and which thus interfere with the ability of the individual to respond normally to environmental stimuli. These may have their origin in the genetic determination of the biological structure of the child, or be the result of trauma during the fetal and paranatal periods.

Genetically determined disorders, sometimes referred to as hereditary or heredofamilial, manifest themselves mainly in so-called metabolic dysfunctions which play a large role in the mental disorders of infancy and childhood. Examples of these disorders are phenylketonuria and galactosuria.

Trauma during the fetal period which may result in mental retardation is usually due to infections or circulatory factors in the mother which affect the fetus. Since the discovery of the effect of German measles, of the factors concerned in mongolism, and of the RH factor, knowledge of the way the growing fetus may be influenced by external factors operating in the maternal organism has increased. Once thought to be due to genetic factors, mongolism is now considered a congenital acromicria, due to deceleration of growth considered to be a result of an environmental factor operating at a critical period of fetal development, the neofetal period. Cretinism, due to a lack of thyroid hormone during fetal development is another such disorder associated with mental retardation.

Paranatal disorders associated with mental retardation are usually due to vascular accidents or oxygen deprivation at birth. A recent autopsy study involving 200 cases of severely mentally deficient patients showed that 35 per cent exhibited evidence of exogenous factors having acted at the time of

birth on a central nervous system which had been normal up to that time.

NIMH grants supported numerous studies in 1960 to investigate those factors related to mental retardation which occurred in the individual between the time of conception and the birth period. In fact, with the accumulation of observations made in the disorder phenylketonuria, and the recognition that "inborn errors of metabolism" are associated with mental retardation, research scientists proposed problems ranging from basic genetics to epidemiological surveys in an attempt to clarify the association observed. Many of these proposals are being supported.

In an effort to gain as much knowledge as possible concerning the biochemical factors involved in the etiology of mental retardation, support is given to research to investigate the mechanisms by which the concentration of various amino-acid metabolizing enzymes are controlled, the relationship of aromatic metabolites to the mental impairment observed in phenylketonuria and galactosuria, the intermediary patterns of metabolism in these and similar disorders, and the possibility of the presence of a brain-liver relationship in these metabolic disorders.

Greatest strides have been made in phenylketonuria. Phenylketonuria is an hereditary metabolic disease characterized by inability of an affected child to utilize phenylalanine, an essential amino acid. As a result phenylalanine accumulates in the blood and is excreted in the urine, together with phenylpyruvic acid and other unusual metabolites. This biochemical abnormality ordinarily leads to severe mental retardation and neuro-muscular instability. Based on a diagnostic evaluation survey supported by NIMH, the incidence of phenylketonuria is estimated by a group of investigators at Children's Hospital, Cincinnati, to be one in 10,000 children born each year. This estimate is higher than those previously reported, and further continuing surveys will be necessary before the true incidence will be known.

It has been found that infants with this disease are normal at birth, having been protected in utero by the mother's normal enzymatic processes. Soon after birth (3 - 6 weeks) the accumulation of phenylalanine or one of its by-products in the blood and tissues interferes with normal brain development. Results from many clinics indicate that treatment with diets low in phenylalanine allows normal physical and mental development. Early treatment is essential, since the progressive deterioration can only be arrested, not reversed after six months of age.

Galactosuria, another disorder resulting from an inborn error of metabolism, is characterized by inability of an affected child to metabolize galactose and lactose normally. A most important recent development in this field is the discovery that this inability is due to the absence in liver and blood cells (probably in all tissues) of a single specific enzyme, which is normally involved in the conversion of galactose to glucose.

Unlike phenylketonuria, reports indicate that the main symptoms of galactosuria appear very early, usually when the infant is one or two weeks old; in 90 per cent of reported cases they were recognized within the first year of the infant's life. Jaundice, persisting far beyond the usual period of so-called physiological jaundice of the newborn infant, may constitute an early sign that more serious trouble is impending. Neonatal bleeding has been reported as an early complication.

Researchers have observed that when galactose is eliminated from the diet of a galactouric infant, the level of galactose in the blood falls quickly, proteinuria cases, and the level of amino acids in the urine decreases to amounts found in the urine of normal infants. Following this, all symptoms gradually diminish and disappear. After such apparently complete recovery, resumption of milk feeding even for a short period may provoke a return of all symptoms, that again disappear when milk is withheld.

There is abundant evidence that in this disorder, as in phenylketonuria, if therapy is begun early the severe physical manifestations of the disease may be prevented, or reversed if already developed, but the complete prevention of mental retardation is less certain. In several reported cases in which treatment began early, the mental development of affected children is said to be normal.

In phenylketonuria, as in galactose disease, the mechanisms responsible for central nervous system damage are not yet clearly defined. It has been claimed that brain damage may occur as a result of secondary deficiencies of essential amino acids or other food elements, or as a result of neurotoxic agents formed as products of the intermediary metabolism of phenylalanine. It appears that after about three years of age the infants who were successfully treated with the phenylalanine-restricted diet can be fed a normal unrestricted diet without risk of further brain damage. It has been noted that the extent of early damage may influence the effect of the deleterious metabolites, as indicated by the fact that older, untreated phenylketonurics with milder biochemical abnormalities can be mentally normal. Such reasoning may apply equally to galactosemic infants who are treated early and develop normally, and to those who are treated late and exhibit evidences of more or less severe mental retardation which persists despite a galactose-restricted diet.

To implement the findings thus far obtained and to evaluate methods of early detection of cases, studies in the Children's Hospital Research Foundation, Cincinnati, Ohio, by Dr. Josef Warkany and a team of associates trained in many scientific fields, continued to receive support to determine the interrelationship that might exist between mental deficiency and these metabolic disturbances as observed in populations of apparently normal and known mentally retarded children. Children studied were selected from clinical services of hospitals and from institutions for retarded children. These studies were also extended in selected cases to parents and siblings of the retarded children to discover both the genetic relationship and the carrier states of the metabolic defects which were not able to be detected through clinical examinations. By applying the newer techniques of paper

chromotography, urine samples from these individuals were studied for the presence of the various amino acids involved in these disorders. In phenylketonuria, it was found that phenylpyruvic acid, one of the characteristic urinary excretory products, is able to be detected very simply by the development of a green color when a few drops of ten per cent ferric chroride solution is added to the urine. It was noted also that in the newborn nursery testing for phenylpyruvic acid in urine does not detect the disease. For reasons not yet known, the mechanism for excretion of phenylpyruvic acid is not always effective during the first week. If treatment is to be begun, however, in time to prevent damage to the developing brain, the disease must be diagnosed as early as possible. Since there are no clinical symptoms in the early weeks, to ensure diagnosis all newborn infants' urine should be tested during the critical age period between three and six weeks.

In an extension of the use of paper chromotography, a screening program of newly born infants was instituted by these investigators for the early detection of metabolic disorders. In this program the squares of filtered paper were distributed to the mothers of infants by attending obstetricians, pediatricians and nurses. Mothers were instructed to place the paper squares in the diapers of the babies at ages four to six weeks, and to return the paper squares, when dried, to the Children's Hospital Research Laboratory. In the laboratory, tests were carried out to detect phenylketonuria and galactosuria, by means of a chromotograph of patterns of amino aciduria. A similar early detection program is receiving support by Dr. Willard Centerwall, at the College of Medical Evangelists in Los Angeles, California. The aim of this investigation is to so establish the efficacy of the filter paper test in early infancy that the method could be used routinely.

Researchers have stressed the fact that the purpose of early detection of infants with phenylketonuria and galactosuria is specifically for the prevention of the observed mental retardation associated with these conditions. Moreover, since it has been found that a low-phenylalanine diet supplied to the young infant suffering from phenylketonuria helps to prevent mental retardation and in the older child to improve retardation, members of Dr. Warkany's team have carried out research in the dietary management of children afflicted with these disorders. Not only did these investigators plan a long-range dietary program but they initiated the child to the diet and indoctrinated the parents of the children so that the therapy would be successful.

The team under Dr. Centerwall in Los Angeles, reports that in treating the phenylketonuric patient by diet, the physician is faced with the problem of controlling the diet as carefully as he would for the diabetic patient. These workers also advise that frequent testing of urine and blood for the presence of high amounts of phenylalanine is of primary importance since the actual amounts of phenylalanine required to maintain blood levels in the phenylketonuric patient appears to vary with each patient.

The scope of this research indicates that mental retardation associated with inborn errors of metabolism may be prevented in the near future. In addition, the research on the underlying mechanism of the metabolic block will, in all probability, elucidate any existing relationship of enzymatic interference associated with other behavioral disorders.

Disorders associated with mental retardation occurring during fetal development are being investigated in NIMH-supported research conducted by a team led by Dr. William Beierwaltes at the University of Michigan. These studies have considerable interest with regard to the prevention and treatment of mental retardation which is associated with congenital hypothyroidism or cretinism. Cretinism is a disease resulting from a lack of thyroid hormone during fetal development. It affects the cerebral cortex with accompanying physical and mental disorders. Until recently it was not considered to be an important cause of mental retardation.

Studies by Dr. Beierwaltes, however, of inhabitants in an endemic goiter area in northeastern India seem to indicate that it may be much more important than had been suspected.

Much of Dr. Beierwaltes' work has been devoted to examining hypotheses dealing with this disease. For example, he has shown that although antibodies are known to cross the placenta from mother to fetus, autoantibodies present in the mother are apparently not a cause of congenital hypothyroidism in the fetus. He has also demonstrated that thyroid hormone can be administered to the pregnant mother in extremely large doses without apparent harm to the mother and yet be successfully transmitted across the placenta to be absorbed by the fetus.

In a specific case, a woman who had previously given birth to two cretins was given dessicated thyroid when she became pregnant for the third time to assist the fetus to develop normally. At the birth of this child, tests showed that the child was normal and that normal uterine conditions had been produced by the administration of thyroid to the mother during her term of pregnancy.

Further studies showed that a fetus may have temporary hypothyroidism, while in utero, which results in brain damage. After the child is born, his thyroid gland develops normally. Thus, the child will be normal physically but mentally retarded to the degree of the temporary non-functioning thyroid during fetal development.

From Dr. Beierwaltes' research has come not only an increasing recognition of the need for diagnosing and treating congenital hypothyroidism early, but the actual beginnings of diagnostic methods for recognizing it at birth or a few weeks afterward. The presence of an umbilical hernia, prolonged cyanosis or a high birth weight (over nine pounds) have been found to be indicative of congenital hypothyroidism at birth. Within a few weeks other symptoms are observed, such as feeding difficulty, retarded growth, prolonged icterus neonatorum, and respiratory distress with cyanosis. Thus, early recognition and treatment may make possible normal development

and life for an otherwise hopelessly diseased group of individuals.

Mental retardation due to traumatic effects to the brain may also result from anoxia during the birth process. This disorder is regarded as one of the primary causes of non-familial mental retardation among human infants. New findings about the role of oxygen deprivation (anoxia) in the etiology of mental retardation have been contributed by a study, supported in part by research grants from NIMH, in which Dr. Gilbert W. Meier, at Vanderbilt University, has further investigated some of the psychological and neurophysiological effects of paranatal anoxia. Working with experimental animals, Dr. Meier demonstrated that the specific effects of anoxia at birth are a function of the severity of oxygen deprivation suffered. From studying newborn white rats, Dr. Meier found that thirty minutes of oxygen deprivation had no effect on brain function but that sixty minutes of anoxia produced significant impairment in learning.

With the progress made by scientists in these areas of mental retardation, indications are clear that in the years ahead many more children will be born with the opportunity to develop as normal human beings.

Learning in the Mental Retardate. Learning on the part of the mentally retarded is an area which presents pressing problems of social adjustment. Research supported by the National Institute of Mental Health is being carried on both in highly structured, well-controlled, laboratory settings and in institutions for the mentally retarded to derive principles of learning as they may apply not only to the problem of mental retardation but to the field of child development generally. The past few years have witnessed a remarkable upsurge of interest in this area of research.

Mental retardation, literally paraphrased, is a slowing of the mind's processes; thought is slowed or incoherently organized; emotional reactions are more inadequate; and action is often slowed or disconnected. On the basis of such symptoms, mentally retarded children have been divided into three levels - the educable, the trainable and the totally dependent children.

The educable mentally retarded children are those who because of slow mental development are unable to profit sufficiently from the program of the regular elementary school. They can, however, learn many things in a special class. Their retardation is such that they are able to learn some of the academic skills, such as reading, writing, and arithmetic. Because they are capable of acquiring second, third or fourth grade achievement by the age of 16, they are called educable.

In contrast to the educable mentally retarded children, those described as trainable are more retarded and can not learn academic skills. Trainable mentally retarded children are those who are developing at such a slow rate that they are unable to profit from the program of instruction suitable for the educable mentally retarded but yet have potentialities for learning self-care, social adjustment in the family and neighborhood and economic usefulness in the home, in a residential school or in a sheltered environment.

Totally dependent children are those who, because of very severe mental retardation, are unable to be taught to the level of the trainable mentally retarded children.

A most interesting aspect of research in learning as applied to mental retardates is the effect of environment. It has been postulated that from a psychological and anthropological frame of reference, insofar as the co-called "familial" retardate is concerned, lack of environmental stimulation is the major etiological variable. The typical familial retardate, it is claimed, is an environmentally deprived individual. The question of what to do about him is thus substantially a psychosocial-educational one and one that will always be attacked incompletely until considerably more is known about the learning process. The modification of behavior by environmental stimulation, while also encompassing motivational, fatigue, and other such phenomena, is substantially a matter of learning, broadly conceived. Manipulation and enrichment of the retardate's environment, it is believed, will remain in large part a trial-and-error affair until a good deal more is discovered about the basic laws of learning relevant to the retardate's behavior.

To make it possible for mentally retarded children to adjust socially to the community in their development, research is being conducted in laboratories and in institutions for the retarded to derive principles of learning as they may apply to the mentally retarded and which can be related to complex, "real life" problems. Factors relating to learning found in the normal child are being used in studying the mentally retarded, since the mentally retarded are simply those individuals at the lower end of a continuum of learning capability embracing the entire population.

In a series of studies conducted in a school for retardates, the effects of verbal urging and praise upon the psychomotor performance in these children were measured. The children in the institution were separated into two groups; one was arbitrarily selected as the "urged and praised" group, the other as the control. Both received the same tasks to do but those in the experimental group were given, in addition, comments by an observer such as "that's fine," "you are doing good," "try to beat your last score," or "try to go higher this time." The findings demonstrate that this type of verbal urging and praise had a facilitative effect on the performance of the mentally retarded. The same finding was obtained when the praise came from a peer. These findings show that verbal symbols, such as good," when signifying social approval, serve as a reinforcing stimulus operating to influence verbal response patterns.

Another series of collaborative studies in this area are investigating the full range and structure of abilities in the retarded. Abilities are being explored in a hierarchy of functions, starting with basic sensory and motor tasks through perceptual functions to reasoning, memory and integrative functions. Conditions leading to more efficient and more complicated discriminative learning will be investigated and findings analyzed in relation to normal children. Emphasis will be placed on motivational variables and on conditions influencing effectiveness. Patterns of functions,

it is hoped, will form the basis of a behavioral classification system which will be useful for research and for educational programming for the mentally retarded. Such a development will be of great value since the education of the retardate is as yet in its infancy.

In determining the factors which enter into the institutionalization of the mildly retarded child, it is important to know the roles played by socio-cultural, constitutional, psychiatric, psychological, educational, and other factors. In one study receiving NIMH support both families and social agencies are being investigated to determine the factors influencing the decision to institutionalize the child. Is institutionalization a factor which affects the self attitude and personality of the mentally retarded child? Answers to this question can come from investigating the differences in self-attitudes between institutionalized and non-institutionalized retardates. The relationship of self-attitudes to motivation in the institutional program, performance in control led learning situations, and progress in occupational and academic training programs are being measured. Another aspect of this problem is being investigated in a comparative study of the personal and social adjustment of mentally retarded children placed in special classes with those who remain in regular classes. Investigators believe that the skills learned by a child are often of relatively little value unless the individual has achieved an adequate level of personal adjustment, has had sufficient social experience commensurate with his capabilities and has learned to make the kind of adjustments in society that will enable him to use the skills he has learned. It is important, therefore, to know the effects of special class programs upon the personality and the resulting adjustment of mentally retarded children.

The role of speech, language and communication in relation to mental retardation is one which has been gaining an increasing amount of interest in the past few years. A number of research projects stand out as holding considerable promise. In one, the biological propensities for the development of speech and symbolic behavior in general are being described qualitatively and quantitatively. Normal and retarded children are being followed in their development from infancy to observe growth of motor coordination and integration of the vocal tract. The development of skills in the use of sentence structure will be studied by purely formal methods together with an investigation of the semantic relationships of speech at various age levels of the normal and of the mentally retarded. In another study, early language developments are being compared among groups of mentally retarded children, one group being institutionalized and the other being in the community. In still another, a language program is being developed for mentally retarded children in institutions. The purpose of this study is to develop techniques of teaching mentally retarded children, diagnostic assessments and tests to measure the verbal characteristics of institutionalized children, and to develop a team program for improving the environmental milieu of the institutional child for the purpose of stimulating verbal development.

An overview of research on learning in the mentally retarded children appears to suggest that the retarded child differs psychologically from the normal only in intelligence, other aspects such as motivation and emotion

representing secondary factors resulting from socio-environmental conditions rather than primary characteristics. Accomplishments to date hold out much hope for the retarded child, particularly those on the educable and trainable levels, and indicate the need to continue and expand studies in this area. In addition, since information on the basic learning processes of the normal child is still quite incomplete, observations leading to the development of principles of learning for the retarded child will assuredly be applicable also to the normal child.

Aging

Among those social problem areas which are of special concern in the research grant program the subject of aging involves, in an immediate, personal context, the greatest number of people. Early in 1961 the White House Conference on Aging will focus some of the national concern with problems of older Americans.

During f.y. 1960, the Institute gave support to 33 research projects on aging for a total of $1,071,778. The range of this program bridges many disciplines and a wide variety of research approaches. Among some of the biologically oriented studies are the effect of aging on the central nervous system, senile degeneration of the brain, heredity of health and mental disorder, and cerebral physiology in functional disorders.

Drs. Armand Loranger and Henryk Misiak of Fordham University's Department of Psychology have been studying the relationship of critical flicker frequency (CFF) to brain pathology, age and intellectual functions. Earlier investigators have noted that the average CFF of groups with brain pathology is lower than the average CFF of normal groups, and thus CFF has been viewed as a potentially useful indicator of the integrity of the central nervous system. In their work with fifty women residents (ages 74-80) of homes for the aged in New York City, Drs. Loranger and Misiak have explored the hypothesis that if there is a correlation between CFF and intellectual functions, the relationship should be evident in old age, and that there should be more pathologically-lowered CFF's in old age than at any other time of life. The investigators administered five tests of intellectual function to a selected group of fifty elderly women who were free of eye pathology, and also tested their CFF thresholds. Their findings corroborated the suggestions of earlier investigators who worked with a small sample of elderly men. The results of all but one of the tests of intellectual function correlated significantly with critical flicker frequency. Tentatively the investigators ascribe the relationship of CFF and intellectual functioning to reduced central neural efficiency, of "alertness", in old age, which adversely affects both CFF and intellectual functions, more especially comprehension of new ideas and adoption of new work methods.

Other studies of the aging process are examining psychological criteria of aging, attitudes of older people to death, social attitudes toward old people, and environmental and personality factors leading to adjustment in aging. Few comparative studies of aging have been undertaken. During

1960, Dr. George Rosen of Columbia University, as part of a larger NIMH-supported research project on the social history of mental illness, prepared a cross-cultural and historical survey on the psychopatholy of aging.* Problems of adjustment to aging, Dr. Rosen noted, are as old as mankind. Ethnographic literature, not surprisingly, indicates that the old have fared worst among peoples whose resources have been limited or for whom dependents are inevitably a burden. Greek literature noted that certain qualities of intellect and feeling represented the gains of old age, i.e., prudence, discretion, wisdom and mature judgment. The Greeks had observed that some but not all, old people might attain that state where health, temper and intellect combined to give a calm, peaceful and perhaps happy old age. Dr. Rosen points to Cephalus' comments on the miseries for which men blame old age: "It is not 'old age' that is the cause, 'but the character of the man. For if men were temperate and cheerful even old age is only moderately burdensome.'" Particularly within the last four decades, Dr. Rosen notes, the ancient view that old age is necessarily a period of deterioration has been replaced, at least on a conceptual level, by the idea that aging and disease are not synonymous. While it is difficult to separate the role of environmental elements, it is evident that environment is more easily modifiable than constitution. Although some impairment may be inevitable in age, the keys to prevention, control and therapy of mental pathology in old people, Dr. Rosen's survey emphasizes, lie not alone in the impaired individual but also, and even more significantly, in understanding the perceptual and social environment in which he exists.

Present-day clinicians often take for granted the adverse consequences of social isolation in the aged, often without establishing this effect under controlled conditions or understanding the mechanisms which bring it about. Dr. Joseph Zubin, Professor of Medical Psychology at Columbia University, and his associates, attempted to explore this relationship scientifically, using as subjects one hundred residents of a home for the aged. In a paper from this study, reported by Nechama Tec and Ruth Granick**, social isolation was defined as "the absence of role relationships which are generally activated and sustained through personal interaction." The amount of contact with relatives, presence of children, length of unemployment period, and mode of living -- i.e., alone or with others -- indicated the degree of withdrawal.

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* George Rosen, "The Psychopathology of Aging, Cross Cultural and Historical Approaches," presented before the Fiftieth Annual Meeting of the American Psychopathological Association, February, 1960.

** Nechama Tec and Ruth Granick, "Social Isolation and Difficulties in Social Interaction of Residents of a Home for the Aged," Social Problems, VII, No. 3 (Winter 1959-60), 226-232.

Dr. Tec's results show that a lack of personal interaction beforehand does indeed hamper subsequent adjustment to a different environment. Furthermore, "isolates" themselves appear to have a disruptive effect upon their new surroundings -- especially if the social system involved is highly integrated.

The paper calls attention to many other areas in need of exploration, including a need to find out the process(es) by which prior social isolation leads to disturbed social interaction -- if indeed it does. The most important mediating factor, the investigators feel, is a "loss of social skills and sensitivity to social expectations," leading to disruptive nonconformity. (More isolates than controls in the study had to be transferred to mental hospitals.) The investigators note that a distinction must be made between "voluntary" or "involuntary" (or enforced) isolation, and that it seems important to determine the causal relation(s) among personality difficulties, social adjustment and social isolation.

Whatever our hopes for prevention of some of the adverse concomitants of old age, geriatric mental problems will continue to be a part of twentieth century society. Researchers are therefore also exploring better methods of care and treatment of psychiatric geriatric patients. Dr. Eugene Burdock* of the State of New York's Department of Mental Hygiene conducted a biometric evaluation of an intensive treatment program at the Geriatric Unit of Central Islip State Hospital. Set up in 1956 as a pilot program of intensive treatment for female geriatric state mental patients, the Geriatric Unit offered psychotherapy, physiotherapy, occupational therapy, and placement services for the patients utilizing its facilities. The patients cared for in the intensive treatment unit were compared in a one year follow-up of a control group of regularly hospitalized geriatric patients. While the results of the study do not identify the specific causes of changes within the groups, they indicated that the benefits of the intensive treatment program were reflected in the overt behavior of the treatment groups. The intensive treatment unit returned over five per cent of the patients to the community about a month after admission, accelerated its release rate to a maximum of ten per cent by the fourth month, and then showed a gradual decline in release rate to one per cent by the end of the year. Eighteen per cent of the patients were out of the hospital after six months and 13.5 per cent were still out at the end of the year. Fewer patients dies in the intensive treatment unit, and even the moribund tended to live longer than the control patients, who received little more than physical care.

To the degree that society is willing and able to finance intensive treatment programs for psychiatric aged patients, it seems clear from this and from other research that a proportion may be reclaimed.

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* E. I. Burdock et al, "Biometric Evaluation of An Intensive Treatment Program in a State Mental Hospital," The Journal of Nervous and Mental Disease, 130 (April 1960), 271-277.

The advent of the psychopharmacologic agents has also given new inspiration for the trearment of geriatric patients. As pointed out by Dr. Reese Jones, of the Institute's Psychopharmacology Service Center's staff in his 1960 survey of drug therapy in the aged*, the available literature indicates that the use of chlorpromazine and related drugs has effected a real change in the usual atmosphere on geriatric wards and in the treatment of ambulatory patients. Dr. Jones' review discusses current trends in drug therapy in aged persons, but notes the difficulties of assessing the direct effect of any one drug in view of the growing appreciation of the influence of social and milieu processes on drug responses.

While research returns in the field of aging give no promise of definitive relief from the difficulties associated with age, even slight gains in a field which affects the entire population may be of immeasurable comfort.

Alcoholism

The problem of alcoholism is being studied both in terms of its psychological and biochemical aspects.

A study by Dr. Robert Olson, Professor and Head of the Department of Biochemistry and Nutrition at the University of Pittsburgh, has attempted to clarify the question of whether alcohol occurs endogeneously in the mammalian tissue. His findings indicate that alcohol (ethanol) has been isolated from the tissues of several animal species in a wide range of amounts. Intestinal bacterial flora, which were questioned by other investigators to be a possible ethanol source, thereby contaminating the tissue samples under study, were excluded as a possible source. Using ethol-dinitro-benzoate, a precursor of ethanol, Dr. Olson was able to show by chromatographic methods that ethanol could be synthesized endogeneously in the liver. Dr. Olson's overall research aims are to test a number of biological factors which might result in the occurrence of chronic alcoholism, including abnormalities in response to alcohol in vitamin metabolism, serotonin release and/or metabolism, and adrenal responsivity.

Since it is thought that the physiologically active substances serotonin and norepinephrine found in the brain are the chemical transmitters regulating autonomic functioning, Dr. Olson and his co-workers studied the effect of acute and chronic ethanol administration on their concentration in rabbit brain stem. Evidence was obtained which indicates that an intravenous infusion of two gram per kilogram of alcohol produces depression of both serotonin and norepinephrine levels in the brain stem of the rabbit. The parallel depletion of both neurohormones persisted long after the alcohol had disappeared, an effect which is reminiscent of the action of reserpine. Chronic administration of alcohol for seven days produced a fifty-percent decrease in both serotonin and norepinephrine levels in rabbit brain stem. If this

* Reese T. Jones, "Drug Therapy in the Aged," to be published in the Transations of the Fifth Annual Research Conference of Veterans Administration Cooperative Chemotherapy Studies in Psychiatry, held in Cincinnati, Ohio, June 1960.

reaction to alcohol is similar in humans, the effect of chronic alcoholism may be such that the levels of these neurohormones become persistently subnormal and the autonomic nervous system repmanently impaired.

The relationship between the serum magnesium level, delirium tremens and other alcohol withdrawal symptoms are of vital importance in the treatment of chronic alcoholics. Work has shown thus far that there is a decreased concentration of serum magnesium in patients with delirium tremens and alcoholic hallucinosis. Whether a serum magnesium deficit results from, or is the cause of, delirium, with its increased psychomotor agitation, disorientation, excessive perspiration and hallucinosis, remains to be determined. However, the findings in a number of delirium tremens patients who were studied during convalescence showed that the value of serum magnesium increased in each case without the use of magnesium in the therapy, thus failing to substantiate the hypothesis that a magnesium deficiency exists in alcoholic patients who have consumed copious amounts of alcoholic beverages and who have had a poor or restricted diet.

In any disorder, research findings leading to an understanding of the etiology of the disorder are the immediate forerunners of prevention or specific therapy. Findings on the genesis of alcoholism have been contributed by a study supported by the National Institute of Mental Health in which William McCord and June McCord, in the Department of Sociology at Stanford University, investigated data which had been gathered on a group of male individuals both before and after the onset of alcoholism in any of these individuals. A longitudinal social study was made of the physiological, psychological and social characteristics of a group of boys and their families. By comparing these characteristics for those in the group of boys who became alcoholics as adults with those who did not become alcoholics, the authors came to the tentative conclusion that the typical alcoholic as a child underwent a variety of experiences which resulted in a battle within himself between his intensified need to be loved and his equally strong desire to repress this need, or as might otherwise be said, which heightened his inner stress, intensified his desire for love and produced a distorted self-image.

The research is based on a sample of 255 urban, relatively lower-class boys who were participants in the Cambridge Somerville Youth Project. Originally selected and observed in the 1930's, these boys were then traced to adulthood. Twenty-nine of the subjects became alcoholics; the great majority did not. By statistically comparing those who became alcoholic with those who did not, the authors distinguished certain psychological, personality and family traits that set the alcoholics apart as a distinctive human type in their childhood, long before the onset of their disorder. It thus became possible to eliminate some of the retrospective biases and confusion that have plagued previous analyses of the problem.

The major findings show that the alcoholic had undergone a variety of frustrating experiences; he was more likely to have suffered from various neurological disorders, and more likely to have been raised in a family disrupted by a high degree of conflict and basic disagreement. Such stress can, of course, be expressed in many ways other than by alcoholism. The major

force which seems to lead an individual under high stress to express his anxiety in alcoholism was the erratic frustration of his dependency desire.

The fundamental conclusion reported is that the typical alcoholic appeared to lack specific definition of the male role, particularly in terms of that male role in American society which, by radio, newspaper, teachers and movies, is depicted as responsible, courageous, law-abiding and loving. The individual who has been subjected to such experience often seeks to resolve these conflicts behind a facade that can satisfy his dependency conflict and his confusion about his self-image and insure the approval of his society. The potential alcoholic, therefore, accepts the American sterotype of masculinity and plays this role to the hilt. By becoming a seemingly highly independent male the individual achieves a temporary resolution of his disturbing conflicts. As an adult, these investigators suggest, the typical pre-alcoholic involves himself in a quest to satisfy his dual desire to be independent and dependent at the same time. Most avenues of expression are closed to him and alcohol becomes a major outlet for such a person since, when intoxicated, he can achieve feelings of warmth, comfort and omnipotence.

It is the belief of the authors that, although the alcoholic begins drinking only at parties and then gradually reaches the stage of blacking out after sessions of heavy drinking, his life becomes oriented around securing his daily supply of alcohol. Further, the confirmed alcoholic increases his intake of alcohol because intoxication satisfies his dependency urges and obliterates reminders of his own inadequacies.

Juvenile Delinquency

The NIMH is supporting a wide range of psychological and sociological studies relating to juvenile delinquency, including studies of family interaction and personality development, studies of street corner gangs and attempts at early identification of maladaptive behavior. In addition, a sizeable number of action and demonstration programs (combined with research and evaluation) are attacking this social problem with the assistance of community clinics, treatment and guidance centers, and a wide variety of voluntary social welfare organizations.

In the area of developmental disorders as they relate to juvenile delinquency, longitudinal studies are receiving support to investigate the role of psychological and social factors in the normal and abnormal behavior of the young child. For example, attempts are being made to establish normative data on the kinds and amount of aggression to be found in children at the pre-adolescent age level and to identify the consequences of such behavior.

One important approach to the problem of juvenile delinquency is an attempt to delineate the epidemiologic vectors of delinquency and its control. Based on the knowledge that a high correlation exists between certain indices of delinquency and social disorganization, studies of the process of social disorganization can lead to information on the cause and spread of juvenile delinquency and the development of effective control programs.

The Joint Commission on Mental Illness and Health

What does mental health mean to the average American? What is the level of mental health in the country as a whole? What is mental health? Answers to these and other questions were sought in a study reported by the Joint Commission on Mental Illness in a volume entitled Americans View Their Mental Health*. Questionnaires were sent to 2,465 Americans over the age of 21, living at home, selected so as to be representative of the total population for such variables as age, sex, education, income, occupation and place of residence.

The fundamental premise upon which the study was based was that each individual has within his life span a given potential for mental health or ill health, depending upon a complex of biological, psychological and sociological forces affecting his behavior. Since these forces relate to the raw materials of which the individual is made, and to how these materials are shpaed and molded through environment and experience, some of which might impose critical stresses, it is recognized that everyone will, at times, experience psychological trouble or feel troubled. The individual may successfully cope with these stresses or fail to do so in varying degree. Thus it was assumed that mental health springs not from avoiding all stress, but from a capacity to accept normal amounts of stress with some ability to rebound or to handle trouble. When the individual feels unable to do so through his own resources, he may or may not seek help from others and he may or may not get it. In order to cover all aspects of the problem, the questions asked by the survey fell into two general categories. The first dealt with the way in which people feel they have adjusted to life and the second, how they have coped with their problems, what motivated them to seek help, where they went for it, and how effective they thought the help was.

The findings were very interesting. Money and other material and economic considerations which could bring the individual material comforts, adequacy of living, and economic security was a major source of happiness or unhappiness. One of the primary sources of happiness to adults were their children. It was clear that well over halp the population finds its greatest happiness in the home, conditioned by feelings of economic security. In fact, it was surprising to find that international tensions, fear of atomic extinction, and the anxious atmosphere of a troubled world did not figure importantly among the things American people say trouble them.

Another important finding in the survey was that the meaning of happiness and unhappiness for American people is not the same as the meaning of worry. Being happy does not imply an absence of worries. This was seen by the fact that most people, almost 95 per cent of the sample, say they are

* Gerald Gurin, Joseph Veroff and Shiela Feld, Americans View Their Mental Health, A Nationwide Interview Survey, New York: Basic Books, Inc., 1960.

either very happy or pretty happy, rather than that they are not too happy, and that at the same time one out of four admits that he worries a lot or all the time. Two out of five worriers blamed money for their troubles.

The authors found some interesting differences between the state of mind of those who worry and are not necessarily unhappy, and those who are unhappy. It appears that unhappy people are pessimistic about the future and the possibilities of change, are apathetic and have a deficit of psychological resources. The happy worrier is likely to be more optimistic about the future, believes things can change for the better, and proceeds accordingly. He is active and positive in his approach to life. Differences in age and educational background were also basic in the comparison of happiness and worry. Younger and better educated people are happier but worry more than those who are older or less educated.

These findings illustrate a major point that any evaluation of relative mental health in different groups depends upon the particular definition of mental health used. For example, if the absence of worry were taken as the criterion for mental health, the older and less educated would be found to be more healthy than if happiness were the criterion. With happiness as the criterion, younger, more educated people would have described themselves as most healthy. The study showed that the differences among Americans are not as striking as the similarities. The factors which differentiate individuals in terms of their capacity for adjustment remain those over which most adults have least control, namely, sex, age and education.

The study attempted to elicit information in the realm of self-perception. It was learned that most people have no difficulty in identifying qualities in themselves of which they are proud, and very few explicitly state that they have none. In general, answers showed that most people are preoccupied with conforming to accepted standards of behavior and that it is difficult for them to construct individual values which differ from the expectations of the general population. However, more than two-thirds wanted their child to be different from them, which leads one to wonder about the security feelings of the average American. In general, the results of this unique study can be summarized as follows:

First, it tends to support other observations that many persons are anxious and insecure. At the same time, it contradicts a general belief that Americans are luxury-oriented and that international tensions and the threat of nuclear war are a significant source of their anxiety. In other words, although it is generally recognized that our culture is highly materialistic, the data indicate that most people seek comfort and adequacy rather than luxury. In addition, it was found that the sources of their anxiety, as people express them, appear to spring from their immediate environment and not from the world at large.

Second, many men, perhaps reflecting the competition between home and job, feel unsure of themselves in their family relationships, on the one hand, and hard pressed on a ladder of status in their life work, on the other.

Their wives, perhaps seeing themselves still cast in a secondary role, may be striving to acheive satisfactions that are not restricted to marriage and child-rearing. These are possible sources of people's distress and unhappiness.

Third, older people are most consistently the ones in the culture who have achieved acceptance of themselves and have learned to live with their personal relationships, their work, and their fate. But this achievement is accompanied by resignation and apathy, and lower happiness and gratification.

Fourth, younger people, especially the well-educated, approach their lives, their relationships with others, and their careers with higher optimism and greater expectations. They possess greater potentials for satisfaction and also for frustration. This is seen in their feelings of greater happiness and satisfaction, accompanied by more problems and self-doubt.

It is important to know how Americans face their problems. A summary of the observations made in this area of the study is as follows:

First, people have more chance for dealing with their troubles when they approach them subjectively, when they see them in internal psychological, rather then external physical terms, and at the same time wrestle with them actively instead of accepting them with apathy.

Second, their ability to adopt this attitude of "healthful worry" is more than any other factor dependent upon education. The higher their education, the greater their self-awareness, the greater their knowledge of channels for help, and, as a corollary to education, the more they can afford to spend on expert, effective help.

Third, most people have to rely on their own resources as they face their problems. When they do obtain help, it is usually informal, expedient, and temporary.

Fourth, the problem of obtaining adequate professional help is a particularly serious one for those in the lower status groups of the population.

Other Areas

An indication of the scope of the research grant program can be obtained from a review of Tables II* and III.

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* Table II on page 11

TABLE III

Distribution of Number of Grant Awards by Primary Field of Study

Field of Study	No. of Grants Awarded	
Psychology	565	
Social Psychology		66
Psychiatry	127	
Other Clinical Medicine	17	
Pediatrics		8
Geriatrics		5
Clinical Neurology		4
Biological & Medical Sciences	141	
Biochemistry		63
Other Chemistry		5
Experimental Neurology		27
Pharmacology		22
Physiology		9
Genetics		5
Pathology		4
Epidemiology		2
Biophysics		2
Anatomy		2
Social Sciences	94	
Sociology		49
Anthropology		37
Criminology		8
Social Work	24	
Education and Training	13	
Administration	12	
Public Health	10	
Information Processing Techniques	8	
Nursing	7	
History	4	
Law	2	
Mathematics & Statistics	1	
Mixed	37	
TOTAL	1062	

To describe to any approximate degree the achievements in all the areas involved in the research grant program is clearly impossible within the limits of this report. Suffice it to say, a variety of significant findings has been contributed from these research areas steadily over the years. Since the structure of man, his environment, and their interaction, result in innumerable complex factors, findings from studies in each branch of science are necessary to reach a conclusion on any aspect of man and his mental health.

III. THE PSYCHOPHARMACOLOGY RESEARCH PROGRAM

During the past year the Psychopharmacology Service Center program has made significant steps in the implementation of program plans initiated during the preceding year. Several special research programs in the clinical area are now under way and a facility for the analysis of psychopharmacological data deriving from research under support has been established. In addition, the number of research projects in the area of psychopharmacology is steadily increasing and the results from these projects are continuing to provide important new information about psychiatric drugs, their clinical effectiveness and their basic mechanisms of action.

A. Psychopharmacology Service Center Program--Administrative and Staff Activities

The staff of the Psychopharmacology Service Center was augmented during the past year by the addition of a social psychologist, a psychiatric social worker, two research assistants and several additional clerical personnel. An administrative position is being created to help handle the increasing load of administration involved in the management of the expanding staff and the expansion of program activities.

The staff continues to provide consultative services to investigators interested in developing research both in clinical and basic aspects of psychopharmacology and to provide scientific informational services to interested investigators.

In addition to these more general consultative and informational activities, the Psychopharmacology Service Center has developed three major special grant programs which are now under way.

(1) A nine-hospital collaborative study of the effects of three phenothiazine derivatives, chlorpromazine, thioridazine and fluphenazine, in the treatment of acute schizophrenic disorders has been organized. Data collection will begin in early February 1961. The study will provide evidence concerning the existence of significant differences in general clinical efficacy and in specificity of action on particular target symptoms of the three drugs under study. Chlorpromazine, the standard widely-used phenothiazine derivative, has a mild sedative effect and produces a significant incidence of extrapyramidal side effects, in addition to having proven efficacy in the control of psychotic symptoms. Fluphenazine, a new phenothiazine derivative, is at least fifty times more potent than chlorpromazine on a mg/day basis, but is reported to produce more psychomotor stimulation and a much higher incidence of neurological side effects. Thioridazine is reported to be effective in about the same dose as is chlorpromazine, but apparently produces almost no neurological side effects. Of the nine phenothiazines now available for prescription use in the treatment of schizophrenic states, fluphenazine and thioridazine appear to be the two which are

pharmacologically most different from chlorpromazine and from each other. Since the hospitals involved in the study range from a private psychiatric hospital emphasizing psychotherapy, through university psychiatric clinics and the psychiatric units of city hospitals to State mental hospitals with comparatively less favorable staff-patient ratios, the study will provide evidence concerning the possible differential effectiveness of these drugs in different hospital milieux.

(2) A special study of the effects of the therapist's behavior on the response of neurotic outpatients to meprobamate and placebo is now under way. The study was planned by the Psychopharmacology Service Center staff in cooperation with investigators at the University of Pennsylvania and Johns Hopkins University. The psychiatric outpatient units of both institutions are participating in this study. This study will be the first to formally test the hypothesis that physicians with a high level of therapeutic fervor induce greater improvement in drug-treated patients than do physicians whose attitude is more reserved and experimental. Further, it is hypothesized that the difference between drug- and placebo-treated patients will be greater in the patient groups treated by the therapeutically-positive physicians. This special study is a portion of a larger special program which is concerned with the effects of psychological set and social interaction upon drug response in both patients and normal subjects.

(3) The third special program involves the broad support of early clinical drug evaluation units. This program aims to improve both the quality and the extent of early clinical drug screening, a crucial step in the passage of promising drugs from the pharmacological laboratory to eventual clinical use. Four units of this sort have received grant support over the past four years, but fail to meet the growing needs of the field. A special announcement of this special program has been made and it is anticipated that approximately 15 applications for the support of early clinical drug evaluation units will be received by January 1, 1961.

Committee Structure. During the past year two Committees on Clinical Psychopharmacology and on Preclinical Psychopharmacology, which are advisory to the Advisory Committee on Psychopharmacology and to the NAMHC, have been established. These two committees work with staff in the development of special research plans and provide preliminary scientific review of special research projects. The clinical committee has reviewed the special research grant proposals involved in the first two special program areas described above and will review applications for the support of early clinical drug evaluation units.

The Advisory Committee on Psychopharmacology continues to work with the staff of the Psychopharmacology Service Center in formulating program plans. The detailed implementation of these plans and the review of resulting special grant or contract proposals is provided by the two committees mentioned above.

The special clinical grant programs described above constitute the major aspect of the past year's work of the Committee on Clinical Psychopharmacology.

The Committee on Preclinical Psychopharmacology has reviewed the research grant program of the National Institute of Mental Health in its area of special interest, utilizing a detailed analysis of this aspect of the psychopharmacology grant program prepared by the staff. In addition, they have been provided with a detailed analysis of published research on the effects of drugs on animal behavior, prepared by a consultant to the Psychopharmacology Service Center. On the basis of its analysis of this material, the Committee has recommended that programmatic support be provided to competent senior investigators, interested in carrying out definitive parametric studies of the effects of a number of standard psychopharmacological agents at appropriate dose ranges on animal behavior, using a variety of behavioral measures. The fragmentary nature of research on the effects of drugs on animal behavior which has been reported in the literature and which is currently supported through the grant program has underlined the need for more extensive parametric studies of the sort described above. The Committee seriously considered the possibility of providing support of this work through the contract mechanism but decided that programmatic support of experienced senior investigators through the grant mechanism would be considerably more productive and effective than the preparation of detailed contract proposals by staff and committee which would then have to be implemented by research institutions which specialize in the contract research field. The likelihood that highly competent scientists could be recruited by such organizations to carry out a highly specific set of procedures designed under contract seemed small.

Informational Activities in Psychopharmacology. The Scientific Information Unit continued its effort to facilitate and improve communication of research findings in the field of psychopharmacology. During the year a large number of bibliographies and reference lists were compiled and distributed. Examples are reference lists on the following drugs: pheniprazine, nialamide, phenelzine, triflupromazine, amphenidone, iproniazid, chlormethazanone, and imipramine. Bibliographies on "research methodology in clinical psychopharmacology,""controlled clinical studies in psychopharmacology," and "the placebo problem in psychopharmacology" were compiled as one contribution to the Center's mission of improving the quality of clinical investigations of drugs. Information on the pharmacological action of drugs was provided in a detailed and annotated bibliography on the metabolism of, and analytical methods for, phenothiazine derivatives used in psychopharmacology. In addition, a large number of bibliographic searches were done, and reference lists compiled in answer to specific inquiries.

The collection of documents, including reprints, books, manuscripts and monographs has expanded considerably. There are now approximately 12,000 documents on file. Much of the activity of the Unit has been devoted to searching the scientific and medical literature, collecting the documents, cataloging and indexing them, and maintaining the document

collection. The collection has been used constantly by members of the Center staff and has been of great assistance to them in providing background information necessary to the special projects on which they are working.

With the increasing number of new chemical compounds of importance to psychopharmacology, it has been imperative to have speedy access to information about them. One major project completed during the year was the establishment of a complete and cross-referenced file of all drugs relevant to psychopharmacology. For each drug, information has been obtained on its chemical formula and structure, chemical name, generic or common name and trade names used in the United States and in other countries. Each drug is also keyed by code number to the document collection, making it possible to retrieve all pertinent reports on it. Keeping this file up to date will be a continuing activity of the Unit.

Because the document collection and dissemination of information encompasses materials in all languages, it has been necessary to provide extensive translation services, both for indexing purposes and for complete translation of documents. The Slavic languages generally present the greatest problems. An expert in Slavic languages was, therefore, added to the staff, and translations of Russian articles are now available.

The Psychopharmacology Service Center Bulletin has been one of the chief means by which information has been disseminated during the past year. The Bulletin is now sent to approximately 3,500 investigators in the field of psychopharmacology, of whom approximately 1,500 are located outside the United States. Of special interest during the past year were the issues devoted to an annotated listing of all NIMH grants in psychopharmacology and tabular presentation of drugs used in psychiatry. The table listing the drugs was especially well received; over five thousand copies have been distributed, many of them for teaching purposes in medical schools.

As part of its attempt to evaluate its own policies and procedures and to contribute generally to the advancement of scientific communication, a small conference was held, under a contract with a private firm, to discuss information needs of scientists. The conference was designed to bring together in a face-to-face meeting several scientists doing research in psychopharmacology and several information and documentation specialists in order to learn whether such a meeting would yield new or fruitful insights into the whole problem of communication.

Although some activities in the Scientific Information Unit have proceeded satisfactorily, it should be pointed out that space and staff problems are acute. Many important projects were delayed, deferred indefinitely, or abandoned altogether purely as a result of the noise and crowded conditions in the office. A recent move has provided slightly more adequate space, but the fact that the Information Unit is now physically far removed from the rest of the Center means that one of its primary purposes, and advantages, has been defeated. To operate most efficiently and to achieve its purposes most effectively, the information function of the Center should be treated as an integral part of the Center as a whole, not as a

separate and discrete operation. The staff is also inadequate for the demands now being put upon it. For example, the Bulletin is written and edited by one person, with part-time supervision. The editing alone is a full-time job. Searching and collecting the literature is also a major task, not one to be handled on a piecemeal basis. Indexing, coding, and answering inquiries are now done by the one professional person in the office, who is also responsible for the over-all direction of the Unit. An attempt to solve some of these problems by contracting for services has been made, but has thus far not been achieved.

The Advisory Committee on Psychopharmacology stated during the year that in the area of scientific information of the Center, a broadened program was extremely important, essential and overdue and deserved all necessary encouragement. It is hoped that during the coming year this recommendation can be put into effect.

Conferences and Meetings. A meeting on Drugs and Community Care was organized by the Center and was attended by some 63 scientists, many of whom were grantees engaged in the study of the effectiveness of drug treatment in the maintenance of psychotic patients in the community. The proceedings included the reports of research results by a number of these investigators and detailed descriptions of a variety of methods utilized by investigators for the assessment of the psychiatric status and the social adjustment in the community of patients of this sort. Other aspects of research design in this area of research were also discussed. The meeting was judged to be quite productive by the participants, the discussion was lively and to the point. Several investigators, who were invited to attend because they were in the process of developing research projects in the area of drugs and community care, felt strongly that their emerging research plans would benefit significantly from the information acquired at the conference.

A similar meeting of grantees and other appropriate research workers and consultants interested in the evaluation of drug therapies for depression is planned for the coming year.

Contracts. The contract mechanism is being utilized by the psychopharmacology program for the provision of services to investigators and for the extension of staff activities in areas where space and personnel limitations and the short-range nature of the work to be done make the contract an appropriate mechanism. At present, contracts are being used for three purposes: (1) the collection of scientific information; (2) the synthesis of chemical compounds; and (3) the provision of data processing, statistical and related research planning services. A contract has been let with Lea Associates, Inc. for the analysis of a body of data from a representative nationwide panel of physicians on the extent and nature of their use of psychiatric drugs to provide the Psychopharmacology Service Center with information which may be utilized in the planning of future research projects aimed at evaluating drug effectiveness in outpatient populations. A contract has also been awarded to the Matrix Corporation to carry out a detailed analysis of the scientific information requests received by the Scientific Information Unit of the Psychopharmacology Service Center. This analysis will lead to an improvement and refinement of the Unit's informational activities.

A contract for the synthesis of chemical compounds related to serotonin has been awarded to Regis Chemical Company and is now in its second year. These compounds are currently being utilized by several scientists in the National Institute of Mental Health and the National Heart Institute as well as by several grant-supported investigators. One compound synthesized under this contract, kynuramine, has formed the basis of a new and simplified method for the determination of monoamine oxidase (MAO) inhibition. This method, developed by Dr. Sidney Udenfriend of the National Heart Institute, now places such determinations within the scope of the usual clinical laboratory available to clinical investigators in most well-equipped hospitals. Previous methods for measuring MAO activity in man required elaborate and complex instrumentation not generally available. Since several antidepressive drugs appear to act through their MAO-inhibiting properties, this new technique provides a simplified method for determining whether patients treated by these drugs are being given a sufficient dosage to achieve the desired pharmacological effect.

A contract has also been awarded to the Temple University Research Institute for the synthesis of a number of phenothiazine derivatives which have been tentatively identified as naturally occurring metabolites of chlorpromazine and other phenothiazines in general clinical use. The availability of modest amounts of such compounds with proven chemical structure will greatly facilitate research on the metabolism of phenothiazine derivatives, since the small amounts of these metabolites isolatable from the urine of patients or animals make positive identification impossible when standard compounds of known structure are not available.

In the two contracts described above and in the subsequent developments of this program, the aim is to support the initial synthesis of chemical compounds which are needed by grant-supported investigators in psychopharmacology and are not available through the usual commercial channels. Once the syntheses have been completed and small amounts of the substances have been made available to interested grantees and research workers at the National Institutes of Health, it is hoped that additional amounts of these compounds will then become readily available through usual commercial channels.

A contract has recently been awarded to George Washington University for the establishment of a data processing unit which will handle data deriving from psychopharmacological studies of special interest to the Psychopharmacology Service Center. This unit will develop computer programs necessary for the analysis of such data and will work with the Center's staff and with investigators referred by the Center to develop efficient plans for the collection and analysis of psychopharmacological data. The Computation and Data Processing Branch of the National Institutes of Health has been providing such help to the Psychopharmacology Service Center and its grantees, but the growing work load had far exceeded the capacity of the Computation and Data Processing Unit to provide the necessary services.

B. Research in Psychopharmacology

As of December 31, 1960, there will be 249 research grants in the area of psychopharmacology, totaling $6,462,819, which have been awarded and will be paid out of fiscal year 1961 funds. Fourteen of these are special grants described above and total $744,482. The amount now committed to the support of active grants equals the total appropriation for the psychopharmacology program in fiscal year 1960 and it is anticipated that the $8,500,000 appropriated for research in psychopharmacology for fiscal year 1961 will suffice to support the additional research grants, both regular and special, being submitted for review during the remainder of the fiscal year.

During the past year a number of interesting findings have emerged from both the basic and clinical projects being submitted under the NIMH psychopharmacology program.

Clinical Studies. There has been a continuing interest on the part of investigators in the clinical properties of the newer phenothiazine derivatives. Freyhan, in a review of his work with chlorpromazine, prochlorperazine, trifluoperazine, triflupromazine and fluphenazine in similar groups of schizophrenic patients, has observed that all of these newer drugs are slightly less likely to produce clinical improvement than is chlorpromazine and that all the newer drugs produce higher incidences of neurological side effects than does chlorpromazine. He concludes that, while the ability to produce extrapyramidal side effects characterizes phenothiazines clinically effective in the treatment of schizophrenic target symptoms, the newer drugs with more marked neurological effects have no major clinical advantage over chlorpromazine. Although comparative studies of this sort carried out on separate patient groups at different periods of time lack the definitiveness to be found in more rigorously controlled studies, clinical investigators with Freyhan's broad experience provide valuable findings which are often confirmed by subsequent controlled studies. The nine-hospital cooperative study described above will provide a rigorous test of Freyhan's general observations. The nine-hospital collaborative study will also test preliminary findings by two grantees, Hollister and Smith, who report that thioridazine, a new phenothiazine which almost completely lacks neurological side effects, is both safe and effective in the treatment of schizophrenic disorders.

A research project carried out with depressed patients from four New Jersey State Hospitals is now comparing electroconvulsive therapy, iproniazid and an inert placebo in a detailed controlled study. Preliminary results on the first half of the total patient sample to be studied reveal two important findings. First, most of the depressed patients in this study, which is, to date, restricted to women between ages 20 and 40, tend to show significant improvement even on placebo medication. Second, both electroconvulsive therapy (ECT) and iproniazid show some qualitative differences from placebo. ECT has shown over-all superiority in total symptom reduction while iproniazid produces a significant speeding of psychological functioning. A similar study comparing imipramine, phenelzine, isocarboxazid and ECT is underway in three Massachusetts State hospitals. A preliminary analysis of the data from this study is now being carried out.

A study of the effects of perphenazine, a new phenothiazine, on the verbal productions of psychosomatic patients at the University of Cincinnati has shown that the drug causes a significant decrease in both overt and covert manifestations of hostility in the total patient group. Patients with substantial amounts of anxiety also showed a decrease in this symptom. The patient group as a whole showed a significant increase in feelings of general well-being.

A series of studies of drugs in neurotic, hyperkinetic and sociopathic children treated in the out-patient clinic at Johns Hopkins University has shown that neurotic children show such a high rate of improvement even on placebo that no significant drug effect can even be expected. Sociopathic children have shown little or no improvement on any of the drugs (meprobamate, prochlorperazine or perphenazine) studied to date. The first two drugs showed little effect on hyperkinetic children. The effects of perphenazine were equivocal. The rate of improvement was not significantly greater than that obtained under placebo, but those hyperkinetic children who improved under perphenazine became worse when the drug was discontinued. Dr. Eisenberg, the investigator who has carried out this research, believes that further research may well identify drugs which are effective in the treatment of hyperkinetic disorders of childhood. This research underlines, however, the present general ineffectiveness in psychiatric disorders of childhood of drugs with generally proven efficacy in adult psychiatric patients.

Basic Research. An interesting comparison of four psychotomimetic agents, lysergic acid diethylamide (LSD), Sernyl (1-(1-phenylcyclohexyl) piperidine HCl), mescaline and Ditran (a mixture of N-ethyl piperidine and N-ethylmethylpyrollidine) has been carried out in schizophrenic and sociopathic psychiatric patients at Ypsilanti State Hospital by Gershon and Olariu. Only one of these, Ditran, produced a clear reactivation of previously experienced acute psychotic symptoms in chronic schizophrenic patients and a delirium tremens-like syndrome in alcoholics with a past history of delirium tremens. Sernyl produced either confused excitement or sedation without hallucinations or other psychotic symptoms. LSD produced visual illusions and hallucinations, but these were milder than those elicited by Ditran and were recognized as drug effects by the patients. Symptoms produced by Ditran were not so recognized. Mescaline, in the dosage used, was almost entirely lacking in psychotomimetic properties. Gershon and Olariu also observed that the effects of Sernyl could be effectively suppressed by intravenous succinate. Ditran is presumed to produce psychotomimetic effects because of its potent anticholinergic properties. This theoretical mechanism of action was strongly supported by the finding that tetrahydroammacrin (T.H.A.), an Australian drug with marked anticholinesterase activity, effectively blocked the severe psychotomimetic effects of Ditran. This group is now examining T.H.A. to see if it has any clinical utility in the treatment of psychiatric patients.

Deanol, a drug being marketed for use in the treatment of mild depressive reactions, has been hypothesized to exert its effect by increasing the amount of acetylcholine in the brain. Doubt has been cast on this theory

by a study of the drug by Freedman and Giarman at Yale. They have been unable to produce significant increases in acetylcholine levels in the brains of experimental animals with this drug.

A study of the effects of dextroamphetamine, meprobamate and placebo carried out by Krugman on psychiatrically normal aged male veterans at the V. A. Center in Martinsburg, West Virginia has shown that both drugs cause significant decreases in the clear-thinking factor of the Clyde Mood Scale. It is interesting that these older subjects reported both drugs as producing undesirable effects while studies of younger subjects using the Clyde Mood Scale have reported generally pleasureable effects from both drugs.

Beecher's group at the Massachusetts General Hospital has studied the effects of amphetamine and secobarbital on the athletic performance, judgment and mood of athletes. The most important finding was that athletes under secobarbital showed poorer performance while judging themselves to be performing better than usual. This disparity between the subjectively perceived and the real effects of the drug could produce dangerous consequences in individuals who drive under the influence of this and related drugs. Amphetamine, on the other hand, significantly improved athletic performance; the athletes showed a slight tendency to believe they had done less well than had actually been the case.

Doctors Ingram and Knott at the State University of Iowa have been studying central nervous system activity as influenced both by lesions and by drugs and have been interested in drugs which produce predictable changes in both central nervous system activity and behavior. One compound, Tremorine, elicits a continuing rest-type tremor in the cat. They have identified the site of action of this compound and are using this well-understood drug effect as a method for gaining further information about the sites of action of other psychopharmacological agents which influence the drug-induced tremor produced by Tremorine. Another compound, imino-beta,beta^1-diproprio-nitrile, has been found to produce a peculiar circling and waltzing behavioral effect in mice which can be reversed by certain psychopharmacological agents. Both compounds produce abnormalities of brain function and behavior against which other psychopharmacological agents can be tested. One of the basic problems facing psychopharmacology has been the necessity of using drug effects on the behavior of normal animals as the major approach to the identification of drugs which will be effective in abnormal states in man. Drugs like Tremorine and imino-beta,beta^1-diproprio-nitrile, by providing specific abnormal behavioral states in animals, may form the basis of promising new approaches to the screening of psychiatric drugs in behaviorally abnormal animals.

C. Future Plans

During the coming year the collaborative multi-hospital study of three phenothiazine derivatives in acute schizophrenic patients will be under way. Preliminary analyses of data collected during this study should provide the basis of detailed plans for subsequent collaborative studies. The special program for the support of early clinical drug evaluation units will be set under way and expanded and additional special studies on the interaction

between drug effects and social factors will be developed. Projects carrying out detailed parametric studies of the interaction between known drugs and batteries of animal behavioral measures will be developed. Some increase in staff to work with the special program areas is anticipated.

Some expansion in the informational activities is also planned. Here it is planned to utilize the contract and special grant procedures to supplement work now going on within the Psychopharmacology Service Center's Scientific Information Unit.

The coming year should also bring about the completion of a number of important clinical studies of the effectiveness of drug treatment in depression and in psychoneurosis. The expanding research grant program should also be productive of a number of interesting new findings in other more basic areas.

IV. THE RESEARCH FELLOWSHIPS PROGRAM: DIRECT AWARDS - PREDOCTORAL, POST-DOCTORAL AND SPECIAL

Throughout the year, applications for fellowships demonstrated that the need for an increased number of scientists qualified for research on mental health problems is nationally recognized, and that a career of mental health research is steadily becoming more attractive. Research training programs in the graduate schools are multiplying, with a differentiation and a sharpening of focus in many fields of research. In medical schools research and training programs which are concerned with mental health problems, though the total number is much smaller than the number of training programs in graduate schools, are expanding vigorously in at least a score of universities, and so providing an opportunity for advanced research training which attracts both the basic scientist and the scientist whose training has prepared him to investigate clinical problems.

The regular, or direct-award, fellowship program of NIMH continues to provide support at all levels, from the first year of graduate study to the scholarly advancement of the senior investigator, for students of research relevant to mental health. The objective of this training may be applied or basic research, clinical or non-clinical. The research fellow may be trained in any scientific discipline or combination of disciplines from which he may secure insight and skills for research in the field of mental health. Research training provided by NIMH represents a balance of approaches from the biological, psychological, and social sciences.

The following table shows the number and distribution of fellowship awards in f.y. 1960, and the expenditures.

Fellowship Level	No. of Awards	Expenditure
Predoctoral	374	$1,224,863
Postdoctoral	113	677,629
Special	29	279,416
Totals	516	$2,181,908

Analysis of the 484 awards in the fiscal year of 1960 may be used to portray the NIMH fellowship program in terms of the sponsoring institutions, the disciplines of the research fellows, and the fields of research in which they are being trained. In f.y. 1960 fellowships were awarded in 69 graduate schools, 32 medical schools, and 27 other research centers of the United States. In foreign countries, 28 institutions sponsored research fellows, including 16 graduate schools, 3 medical schools, and 9 other research centers.

Of the 484 research fellows who received awards in f.y. 1960, 292 were psychologists, 79 were biological scientists, 85 were sociologists or anthropologists, and 22 had degrees in medicine.

The largest group of these NIMH fellows, numbering 178, are specialists in research on the physiological bases and correlates of behavior. This group includes physiological psychologists, physiologists, biochemists, geneticists and other basic medical scientists.

One hundred thirty fellows are studying the social processes which affect human behavior, including interpersonal relations, group processes, social maladjustment, and the social factors in mental illness.

Sixty-six of the fellows are investigating clinical problems or related problems in the fields of personality and development.

Other fields of research, in experimental psychology, education, and medical history, account for 124 of the fellows who received awards in f.y. 1960.

Of the 130 fellows in social science fields, 36 were social psychologists, 46 were anthropologists, 39 were sociologists, and 9 were social workers. During the preceding year (f.y. 1959), 12 awards had been made to anthropologists and 16 to sociologists. Applications from anthropologists, interested mainly in studying problems of culture and personality, were stimulated by an NIMH program announced in June, 1959, whereby the expenses of field training may be provided by research grant supplements to the fellowship awards. Grants totalling $60,000 were approved for 16 research fellows in anthropology in 1960, for field investigations in the United States, Mexico, South America, Africa, India, and the islands of the Pacific.

In 1960 the number of special fellowships increased to 29, from 16 in 1959. From a very small percentage of awards and expenditures during the years preceding 1959, the special fellowships are now approaching a demand for approximately 20 per cent of the funds available in f.y. 1961. Special fellowships are awarded to university faculty members to provide for interdisciplinary or cross-cultural training or for scholarly investigation in preparation for future research. They are also awarded to psychiatrists and other medical scientists who need a limited period of research training after completing their residencies, and to experienced practitioners in various mental health fields who need a concentrated period of training for the pursuit of research objectives.

In 1960, it became apparent at NIH that the method of reviewing applications which had been used since 1948 was no longer feasible. Scientists working in the intramural or extramural programs of NIH had contributed their services to research training by accepting membership on fellowship review panels, which were scheduled for monthly meetings. When, during the spring and summer, the agenda swelled to forty or fifty applications per meeting, and there appeared to be only a slight prospect of relief during the fall months, it was decided that fellowship applications, like applications for research grants, should be reviewed by committees of non-governmental scientists. Review committees were appointed in the fall of 1960, to begin work after January 1, 1961. The three committees which will be assigned most of the applications for NIMH are similar in composition and are designated the same as the research grant study sections in experimental psychology, behav-

ioral sciences, and mental health.

Since the purpose of the NIMH fellowship program is to train scientists for research in the whole field of mental health, and since the potential of this research demands a much larger number of qualified scientists than is now available, growth of the program, as training facilities permitted, has been encouraged. In f.y. 1959, the number of applications was 438, and the number of awards 287; in f.y. 1960, there were 764 applications and 484 awards. In f.y. 1961, based on the experience of the period from July 1 to December 1, the number of applications will increase to at least 1,000, and the number of awards may be estimated at 760. This dramatic growth creates a problem which must be solved either financially or by a curtailment of the program. For the current fiscal year, the appropriation for regular fellowships was increased by only .04 per cent. As a result a cut-off point has been established for fellowships approved in the second half of 1960, which restricts the number of new awards to approximately eighty per cent of the number recommended for approval. In the spring, or fourth quarter of this year, the lack of funds to pay approved fellowships will be much more severe than in the first nine months. Even if the 20 per cent cut-off point is sustained, it is estimated that nearly 300 fellowships will be recommended beyond the capacity of the f.y. 1961 funds. Whether these 300 fellowships may be awarded must depend upon whether the necessary funds will be made available from the appropriation for f.y. 1962.

V. THE MENTAL HEALTH CAREER INVESTIGATOR GRANT PROGRAM

In future years, mental health career investigator grants will be replaced by special fellowship grants, which are described below. Since announcements of the new fellowship grants were not authorized until October, 1960, it was decided earlier that the career investigator program should be continued throughout fiscal year 1961; and in August announcements to this effect were sent to departments of psychiatry and to other sponsoring departments or institutions.

Since the program began in 1954, career investigator grants have provided the opportunity for a highly selected group of young scientists to devote themselves for several years to preparation for independent research in psychiatry and related fields. Eighteen of the grants have been awarded to psychiatrists. Three grants have been awarded to psychologists, and two to internists. The fact that the major objective of the program has been to strengthen psychiatric research by assisting psychiatrists to become investigators explains the predominant discipline. Behavioral scientists other than psychiatrists, however, who bring skills and insights from the biological, social or psychological sciences to psychiatric problems and who may benefit significantly from extended postdoctoral training in a clinical setting, are regarded as appropriate candidates.

In the spring of 1960 grants were awarded to two candidates new to the program, and continuation grants were awarded to three investigators currently receiving support. Grants for twenty-three career investigators have now been awarded since the inception of the program, 19 for five years, 2 for three, 1 for four, and 1 for six years.

To the end of 1960, the total expenditure for the twenty-three grants was approximately $2,000,000, which means an average total grant cost of nearly $87,000. This expenditure includes an average stipend, in the year 1960, of $10,000, an average research allowance of $4,850, and additional allowances to four of the current investigators for psychoanalytic training averaging $2,800.

The grants have been awarded to twelve psychiatric departments in universities, four university-affiliated hospitals, one school of public health, and one private psychiatric institution. Six investigators have been sponsored by three of the research hospitals affiliated with Harvard. Departments of psychiatry at ten other universities have each sponsored one career investigator (Boston University, Rochester, Baylor, Cincinnati, Western Reserve, Maryland, Tulane, Pittsburgh, Yale, and Albert Einstein), and one grant has been awarded to Michael Reese Hospital, affiliated with the University of Chicago. The departments of psychiatry at UCLA and at the University of Pennsylvania have each sponsored two career investigators, and UCLA has shared in the training of two others. The career investigator sponsored by Yale has received one year of training in psychopharmacology at NIMH.

Of this group of twenty-three, 16 were still in training at the end of 1960. Of the 7 who have terminated grants, 4 are directors of research in psychiatric departments at Boston University, UCLA, the University of California in San Francisco, and the Massachusetts Mental Health Center. Two of the alumni have research positions at the Children's Medical Center in Boston and in the psychiatric department of the University of Cincinnati, and one alumnus has gone into private practice. During the current fiscal year, the grants of six investigators will be terminated. Full time research and teaching positions will be provided for this group at the Massachusetts General Hospital, the Children's Medical Center of Boston, and the departments of psychiatry at Western Reserve, Rochester, UCLA, and Pennsylvania.

The career investigator program is enjoyable as well as professionally stimulating to those who have shared in it, including past and present members of the Selection Committee and NIMH staff members, because of a common enthusiasm for the program's objective, a pleasure in the tangible achievement both in terms of individual success and in terms of the total impact on psychiatric research and training, and a lively group spirit, which has been cultivated by annual meetings of the whole group for informal discussion of projects, problems, and principles. The third of these conferences was held at Edgewater Park, Mississippi, in April, 1960. The fourth is planned for April, 1961 at Arden House, Harriman, New York, where the first two conferences were held in December, 1957 and in March, 1959.

At the seventh annual round of meetings, in December, 1959 and in January, 1960, the Selection Committee concluded that on the basis of experience with the career investigators, a new program should be recommended to the Council which would provide for adequately trained scientists positions in which they would be free to concentrate upon research and the related activities of an academic career. In March the Council approved the recommendation for an extension of the career investigator program. Later, as formally

announced in October, this proposal materialized in the form of the senior fellowship grants and the career research professorships, which have been authorized for all of the Institutes of Health and the Division of General Medical Sciences.

It is probable that four of the current career investigators, whose grants will terminate in fiscal year 1961, will be immediate candidates for senior fellowships, and that one former investigator will be a candidate in 1960 for a career research professorship.

At the seventh round of meetings the Selection Committee also agreed that some psychiatric programs have now realized the capacity to motivate and direct residents toward academic careers, and that residents of good endowment for scientific work now have the chance to express promise in research before their residency training is completed, without the necessity of discovering a research interest by a separate period of study or apprenticeship. It follows that a significant number of residents are now ready, in their third year, to plan career investigator training, and that career investigator or special fellowship grants may, in the future, be extended to younger men.

In the fall of 1960, the closing date for career investigator applications was postponed from November 1 to December 15, and a second round of applications during the current fiscal year, with a March 1 closing date, has been announced. It is not unlikely that as many as twenty applications will be submitted by March 1, and that a heightened interest in research careers among departments of psychiatry will be manifest by an increased number of career investigator awards.

VI. THE SPECIAL FELLOWSHIP, SENIOR FELLOWSHIP, AND CAREER RESEARCH PROFESSOR GRANT PROGRAMS

The three programs by which grants will be awarded to institutions (1) in order to provide for advanced training which will lead into careers of research, and (2) for the purpose of assisting institutions to stabilize careers of research, were made available in October, 1960, from each of the Institutes of Health and from the Division of General Medical Sciences.

For NIMH, special fellowship grants will replace the career investigator program, providing for the same type of applicant essentially the same privileges of a three to five-year period of advanced training. Stipends will be individually determined; the maximum annual allowance for research costs of $5,000 is approximately the average for career investigators; and NIMH may continue to provide allowances for special training costs, including the costs of psychoanalytic training. Special fellowship grants may be awarded for training in other than psychiatric departments, and to institutions other than medical schools or psychiatric hospitals. It will be the task of the Selection Committee and the NIMH staff to decide upon objectives, qualifications, and conditions for the special fellowship grants which will constitute an expansion of the present career investigator research training program.

Unlike the career investigator grants, special fellowships will be restricted to citizens of the United States and to immigrants who have filed declarations of intent. The career investigator program will continue until July 1, 1961.

The broader and more flexible of the two research-position programs, the senior fellowship grants, will go far toward fulfilling the need recognized by the Selection Committee and the Council during the past year. These grants may be awarded for staff positions at any level and in any type of department with a research program worthy of support from NIMH. The candidate's minimum qualification is five years of postdoctoral experience relevant to a research career. NIMH may divide the expenditure for a senior fellow's salary and research program with the sponsoring institution. A senior fellow who devotes the major part of his time to research will be free to engage in such related activities as clinical practice and teaching.

Since the October, 1960 announcement, the response to the senior fellowship program has been enthusiastic and widespread among departments of psychiatry, graduate departments, schools of social work with established research training, and psychiatric hospitals with research programs. Senior fellowships are in demand for various purposes: to secure additional staff members, to rescue scientists whose incomes are dependent upon project grants, and to free potentially creative scientists from burdensome activities unrelated to research.

Although the duration of senior fellowships is restricted to eight years (grants may be awarded for five and renewed for three years), the need for the positions is keenly felt, and tentative or definite plans have already been made in many departments to submit applications by December 15, 1960, or by March 1, 1961.

During the first year of the program, career research professorships may be awarded only to medical or osteopathic schools, dental schools, and schools of public health. The schools are invited to propose candidates who are acceptable for full or associate professorships, and who are distinguished in research. A maximum salary of $25,000 may be awarded, but the candidate may receive no income in addition to his stipend from NIH. Schools are invited to submit no more than four applications. The career professor grant is attractive both in financial benefits, including up to $10,000 annually for research costs, and in security, since it may be renewed indefinitely at five-year intervals.

Because of the initial restriction of four applications per year, it seemed doubtful when the program was announced that more than four or five applications could be submitted from departments of psychiatry to NIMH during the first year. By December 1, however, word had come from six universities that the deans of the medical schools had made tentative or definite promises to sponsor candidates in psychiatric departments.

Applications for the research-position grants as well as for career investigator grants will be reviewed by the NIMH Selection Committee. Anticipating much larger number of applications and site visits, the staff planned with the chairman, Dr. John Romano, to enlarge the Selection Committee, which

in October consisted of five members, including three psychiatrists, a psychologist, and a neuophysiologist. Three new members have been recruited, including a sociologist, a psychologist, and a biological scientist; and it is hoped that a fourth psychiatrist will be recruited who will bring the membership up to nine for the current year.

During the current fiscal year career investigator grants will continue to be paid from research grant funds. Salaries for senior fellows will be provided at least in part, from the fellowship appropriation, and research costs for senior fellows as well as for career professors will be paid from research grant funds. For career professorships there is a generous appropriation of $300,000, which is probably in excess of the amount needed for awards in f.y. 1961. It is hoped that the appropriation for f.y. 1962, both in the allocation of research grant funds for allowances and in the allocation of fellowship funds for stipends or salaries, will provide adequately for the new fellowship-grant programs.

TRAINING BRANCH

Annual Report for Calendar Year 1960

The year 1960 was primarily a year of consolidation in the training program. While the appropriation was increased over that described in the annual report for 1959, no basic changes were initiated in the operation of the program. However, a number of program activities which were begun in 1959 were further advanced in this last year. This includes both administrative changes as well as program developments.

I. Program Administration

A. Adjustment of Beginning Dates of Grant Awards

Funds to initiate the plan of advance notification of grant awards were first made available in 1959, as described in the annual report for 1959. The $3,850,000 in the fiscal year 1960 budget was used to finance advance notification for grants in psychology and to schools of public health for training in mental health. This year an additional $11,114,000 was made available in the budget for fiscal year 1961 to complete the procedure of advance notification for all graduate grants. It should be noted that this amount was approximately $2,000,000 less than had been requested to complete this procedure for graduate grants. As a result, some grants among the categories of pilot projects and research training in the biological sciences, which were already on a partially advanced beginning date, were not further advanced. In addition, some of the funds made available for program expansion beyond the fiscal year 1960 level had to be used to complete the payment for advance notification. The following chart shows decrease in the percentage of graduate grant funds awarded after the beginning date as a result of the shift to prepayment.

Fiscal Year	Funds Available (Excluding Funds for Prepayment)		Awarded After Beginning Date	
	Appropriation	Graduate Program	Amount	Percentage of Graduate Total
1959	$18,213,000	$14,863,000	$13,000,000	87%
1960	$22,356,000	$18,806,000	$15,000,000	80%
1961	$28,356,000	$24,391,000	$12,350,000	51%
1962	$28,356,000	$24,391,000	0	0

No provision has been made as yet to move undergraduate grants to this procedure of prepayment. While there has not been the urgency of need for prepayment among these grants, a shift to prepayment should be accomplished eventually, so that the entire program will be on the same payment basis.

B. Distribution of Training Grant Funds

The allocation of funds for this year was complicated by the change in the review and approval procedures and because funds were being used to pay for more than one cycle of applications. Effective September 1, 1960, the regular closing date for receiving applications was changed from December 15 to September 1 of each year. For the closing date of December 15, 1959 applications were accepted only from current grantees applying for continuing grants beginning July 1, 1960. Except for grants in psychology and public health mental health, which were paid for out of the special fiscal year 1960 appropriation of $3,850,000 for advance notification, these applications were to be paid for out of fiscal year 1961 funds.

At the same time, all applications for graduate grants received for the September 1, 1960 closing date had to be paid for out of fiscal year 1961 funds. These applications included all continuation requests and new applications for a beginning date of July 1, 1961. In effect, then, the appropriation for fiscal year 1961 is being used to pay for almost two complete years of awards for graduate grants.

As a result of the complications of this transition into the new review and approval cycle, data were not available for making any changes in the percentages used for distribution of training grant funds among the seven major areas of training. As described in the annual report for 1959, the new procedure for distribution of funds is dependent on three sets of data: (1) Past performance, in terms of training activities supported by NIMH grants for the preceding fiscal year; (2) The present expressed needs of the field for additional grant support as represented by total requests for grants in the year in question; (3) The proportion of these expressed needs identified as meritorious by the Training Committee as represented by approved requests in the year in question.

Information on the second and third sets of data were not available at the time that a determination needed to be made about distribution of funds. Instead, the same percentages were applied as were used last year and in the same modified way (i.e., only for funds available for program expansion beyond the cost of the continuing program).

C. Staff Operation

Early in the spring of 1960 the entire problem of staffing needs in the Training Branch was thoroughly considered. At that time, the following comments were made:

"The size and complexity of the training program are such that this number of persons is not sufficient for present operations, much less for future needs, The staff is so overburdened there is very little opportunity for the thoughtful planning necessary to cope with a worsening situation. This becomes an even more urgent problem in terms of the expected increase in size and activities of the program next year, the year after, and beyond.

"The need for staff increases relate to: (1) Lack of time for present staff of training specialists to make all the necessary site visits. Approximately one-third of the visiting will not be possible in the fall of 1960, with the present number of training specialists. (2) Lack of time for unhurried and careful consideration of important facets of program planning. The pressure of day-to-day activities precludes participation of the professional staff in any but the most immediate and urgent planning. (3) Insufficient professional staff to allow for division of responsibilities and specialization, so that there will be continuity and coordination of administration in all major areas of the training program.

"At the time that statement was made the staff included nine professional persons, eight secretaries, and two technical assistants. The needs were outlined as follows:

In 1960, or as soon as possible:

(1) Two additional psychiatrists for a total of four. One of these would be a senior person to serve as Assistant Chief of the Branch.
(2) One administrative officer as soon as possible.
(3) One training specialist in the biological sciences.
(4) One training specialist in the social sciences.
(5) One additional psychologist this year for a total of three.
(6) One additional nurse specialist in 1960 or early 1961.
(7) One junior professional person for program analysis, plus an additional person at the technician level.
(8) A minimum of three additional secretaries, one for the two specialists in psychiatry, one for the administrative officer, and one for the two training specialists in the biological and social sciences.

In 1961 or 1962

(1) One additional psychiatrist in 1961.
(2) One additional psychologist in 1961.
(3) One additional social worker in 1962.
(4) A minimum of two additional secretaries, to be used among these additional professional personnel."

Recruitment efforts to fill these positions has been partially successful. As of December 1, 1960, three additional professional persons have been added; Dr. Clark Vincent, a training specialist in the social sciences, Dr. Harold Basowitz, a training specialist in psychology,

and Mr. Roger Robertson, a social science analyst in program analysis. Two secretaries and a junior research assistant were also added to the staff. In addition, Miss Rose Hayes replaced Miss Dorothy Gregg as training specialist in nursing. Continuing efforts are being made to bring the staff up to the strength necessary to cope with the increasing administrative responsibilities of a growing program.

During the months of February to May, 1960 Dr. Dale C. Cameron was temporarily assigned to the Training Branch. Dr. Cameron acted as a training specialist and reviewed and visited the pilot project programs.

With the staff growing to a size where individual communication among staff members and with the Chief of the Branch is no longer efficient on an informal basis, steps are being taken to develop a more formal table of organization. This is presently in process.

In program analysis there are presently three major areas of activity: (1) IBM coding of pertinent data about all grant awards from the beginning of the program through the present. In addition, collaborative work is in process with the Statistics and Analysis Branch of DRG in establishing procedures for information storage and retrieval on present recipients of training stipends. (2) Specific projects for obtaining information about individuals who have obtained benefits from training grants. This includes surveys of past trainees, as well as data on recipients of postgraduate education in psychiatry for general practitioners, and reports on internship training in psychology. (3) Collecting and organizing manpower information on the mental health professions. This includes not only collecting available resource material but initiating procedures for developing new sources of information.

Under item (1) above, the coding of the grant awards was used to prepare a publication of a listing of mental health training grants for fiscal year 1960, as was done in 1959. This detailed listing of grant awards by State and institution gives data on the number of stipends and the amount awarded to each institution for trainees, as well as the teaching costs for individual mental health training grants. Summary tables by State and by area of training are also provided. Last year this publication was widely distributed to grantee program directors as well as the information officers of universities, medical schools, and national mental health organizations. The same distribution is being made this year. Another project was the coding of information about individual trainees from the statement of appointment forms. All statement of appointment forms for fiscal year 1959 and 1960 were coded and punched in the fall of 1960. Summary statistics on these data will be developed very shortly.

Under item (2) above, a survey has recently been completed on a 25% random sample of the almost 8,000 persons who received financial support in the period from the initiation of the training program in

July 1947 through August 1959. Completed returns were received from 91% of those surveyed. The data include information on: undergraduate and graduate professional education, present employment status and location, the major professional functions being performed, major fields of professional interest and activity, as well as some of the more usual census data. A report is presently being prepared on this survey. This project represents the first in a series of annual surveys which will provide both cross-sectional and longitudinal descriptions of the professional characteristics of former trainees.

Another project under item (2) above is an analysis of the characteristics of the physicians taking postgraduate education in psychiatry in our general practitioner program. A brief questionnaire has been routinely sent out to the training centers, to be filled out by the physicians. This includes information on their medical education and present specialty as well as age, sex, and address. These are now being coded and a brief report will be made on the results of this survey.

Under item (3) above, a basic library of documents on manpower is presently being compiled. This includes reports and publications on manpower studies in the mental health fields, as well as some more general manpower information. The Training Branch has also been involved over the past year in a project to develop improved manpower data in the mental health fields. With the publication in 1959 of Albee's comprehensive monograph on Mental Health Manpower Trends, the need was highlighted for more adequate procedures for obtaining current and coordinate mental health manpower data. A meeting was held in April 1960 to examine scope and adequacy of the present output of mental health manpower information and to discuss procedures for improving the collection of such information. The sixteen participants included representatives from the four mental health professions as well as other organizations and agencies directly or indirectly concerned with mental health manpower information. Staff representation from NIMH and the Director's Office, NIH, was included. The group discussed the present status of manpower information, and the areas in which there is a serious lack of information. There is presently no coordinated effort to obtain manpower information for the entire field. After discussing the entire situation, the group recommended that a working party of members from the professional associations and other key agencies, plus representation from NIMH consider actual procedures to implement a program of improved data-collection.

A meeting of the working party is taking place on December 16-17, 1960. A contract has been negotiated with an outside research organization to serve as a resource group and secretariat for the meeting. A staff paper will be prepared, evaluating in detail the present state of data-collection and providing a plan for initiating improved data-collection. This plan will be discussed at the December meeting, as a result of which the plan will be revised as necessary. The staff paper and the results of the deliberations at the December meeting of the "working party" will

be made available to all participants at last April's planning meeting. In addition, plans will then be made for whatever seems to be the next appropriate step. It is hoped that with this meeting it will be possible to come a little closer to planning for more adequate manpower information.

D. Coordination Within NIH Training Programs

The Training Branch has been actively cooperating in the plans for coordinating the various training programs at the NIH. Early this spring an Assistant Chief for Training Grants was appointed to implement the coordination of the training programs and to provide for the necessary central information and central services on all the training programs of NIH. The DRG has been made responsible for the central management aspects of the training programs and for the development of common administrative policies and procedures where these affect more than one Institute.

Over the past year, the Training Branch has cooperated with the staff of the Assistant Chief for Training, DRG, in furthering the efforts to implement this coordination among the various training programs. These efforts have consisted of a series of meetings concerned with the development of a new graduate training grant application form as well as various discussions about the present administrative procedures regarding receipt of applications. This has been necessary because the new office of the Assistant Chief for Training, DRG will be responsible for central receipt and distribution of applications. In connection with all of these considerations, the matter of individual policy differences among the various Institutes' training programs has come under scrutiny. Some of the specific matters under consideration relate to the payment of indirect costs, stipend levels for trainees, and payment of tuition and fees. No resolution of any of the issues has yet been achieved. However, the objective is to achieve some uniformity of basic policy, wherever such uniformity does not work to the detriment of the goals of the individual training programs.

II. Program Development

As of the writing of this annual report, no new grants for fiscal year 1961 have yet been awarded. As noted previously, the review and approval procedure was modified this year and all applications for the closing date of December 15, 1959 were for continuing grants, since all new grants with a beginning date of July 1, 1960 had been approved and paid for out of fiscal year 1960 funds and were already on an advance notification basis. As a result, it is not possible to talk about actual new program development. It is appropriate, however, to note that in excess of $10,000,000 worth of applications for new grants were received for the September 1, 1960 closing date, and will be reviewed by the NAMHC in March 1961, for programs beginning July 1, 1961.

The specific details about program development insofar as it concerns new and expanded directions of the program is, therefore, not changed from last year. There are, however, some further comments that can be made about the various areas of support.

A. Training in Biological and Social Sciences

The support in these two areas for 1960 was about $1,300,000, with over $900,000 in the biological sciences and almost $300,000 in the social sciences. It is expected that this year will produce further expansion in these areas.

The grants now active in these two areas include mainly interdisciplinary efforts to increase the utilization of the research skills of biological and social scientists to work in the mental health field. It is felt that this kind of interdisciplinary approach is more and more being brought to bear on mental illness problems and additional trained persons are critically needed. In addition, such individual areas as psychopharmacology are in urgent need of additional personnel and efforts are being made to increase the production of trained persons in this area.

With the establishment of two permanent subcommittees, one in Biological Sciences and one in the Social Sciences it is expected that a more definitive set of policy statements will be developed to guide the growth in these two new areas of support. At the April 1960 meetings, the Subcommittee on Social Sciences discussed the wide diversity of training activities which fall in this area and there was agreement that there should be a broad interpretation of the mental health relevance of such programs. There was also general agreement that, wherever possible, students in training programs of social sciences should be introduced to some of the bio-social problems in the mental health area during the course of their training.

The Subcommittee on Biological Sciences, in its April 1960 meeting, stressed the importance of having basic medical sciences involved in training programs for mental health personnel. It was also recommended that efforts be made to place greater emphasis on the development and utilization of research facilities and stipend awards at the pre-doctoral level so that medical students, prospective research psychiatrists, and other trainees in the medical sciences be introduced to the knowledge and techniques of the biological sciences at an early stage in their careers.

B. Psychiatric Training of General Practitioners

When this program began in 1959, it was initiated under some pressure of time and with earmarked funds totalling $1,300,000. In order to move the program as rapidly as possible, applications were received without regard to closing dates and were reviewed by ad hoc

panels. The entire $1,300,000 was awarded. In 1960, as a result of the first year's experience, a comprehensive set of instructions was developed and three closing dates were established, July 1, 1959, November 1, 1959, and March 1, 1960. The interest in the program continued strong in fiscal year 1960 and a total of $2,300,000 was awarded in 100 grants distributed among 29 states, plus the District of Columbia and Puerto Rico. Of this total, over $1,855,000 was distributed to support 181 residency training awards at an average stipend of approximately $10,250 each. The remainder of over $400,000 was awarded for postgraduate education and training for general practitioners.

This program continues to be received enthusiastically in the field and for fiscal year 1961, $3,800,000 will be awarded. A single closing date of September 1 each year has been established, as for the rest of the program. There is also the possibility that within the next year or so these stipends may be awarded to the training institutions without individual review of the trainee applicants, which would then be in keeping with the procedure for regular residency training stipends.

The present indications are that these grants can add a significant number of specialists to the psychiatric manpower pool and broaden the psychiatric education of the general practitioners. The present number of residencies awarded in current grants of this type represents considerably less than one-half of 1% of the physicians now in general practice. It is not yet possible to predict the level at which this program can be stabilized, but all indications suggest a continued increasing interest in these training grants with corresponding potential for growth of the program.

C. Pilot Projects

These projects had been initiated in 1954 in an effort to develop new ideas in training, to encourage experimentation with training programs in mental health disciplines both at the professional and subprofessional levels, and to introduce mental health content into related disciplines. Because a number of pilot grants are now reaching the termination of their support and because there is no clear mechanism for continuing support, this entire area of support was discussed in some detail at the October 1960 meeting of the Policy and Planning Board of the Training Committee.

Data were presented to the Board which showed that: (1) The approval rate for pilot applications had declined from an initial high of more than 70% to its present level of less than 10% approvals; (2) During this period the application rate had not changed. The trend seems to be alternating peak years; (3) Most of the approved applications were initiated either by staff or members of the consultant group.

It was noted that the decline in approval rate may reflect the decrease in staff responsibility for the pilot area that has accompanied the increase of program support in the separate disciplines. This decline in approval rate does not tell the entire story, however, because many of the requests that were formerly considered as "pilots" are now reviewed and approved within the support in the core disciplines as a by-product of the broadened programs in nursing, psychiatry, psychology and social work, and are, therefore, not labeled "pilot" projects.

There was extensive discussion about how this area might best continue to serve as a stimulus for new methods of training. Continued efforts will be made to maintain good communication with the field so that new ideas can be translated into suitable pilot projects.

One example of the kind of pilot project which has been supported is a project for the development of a teaching and training program in the field of juvenile delinquency at the Judge Baker Guidance Center in Boston, Massachusetts. This project was begun five years ago. The aim in this pilot project was to develop a training program, using the field experiment method, which would expand on existing professional training programs in the mental health professions and allied disciplines, by providing comprehensive field training in the care and treatment of the delinquent child. In so doing, the goal of the project was to recruit and train future workers in mental health professions for work in the area of juvenile delinquency, as well as to enrich the education of other professionals whose role in the community might bring them in contact with juvenile delinquents, and to provide inservice training for such personnel as probation officers, police, and group workers. A very detailed and comprehensive three-volume report of this project was recently prepared which summarizes the progress to date.

D. Other Program Expansion and Change

In the annual report for 1959, it was noted that program development had been minimal because a major proportion of the budget increase for fiscal year 1960 had been used to pay for the cost of adjustment of project period dates and the increased rates in trainee stipends, plus payment of tuition and fees and teaching salary increases. And for this year, as has been noted, applications were received for a September 1, 1960 deadline, with a beginning date for the grants of July 1, 1961. In effect, then, there has been a two-year lag in new program expansion.

This disruption in program development is primarily the result of moving all graduate grants to a procedure of advance notification. It is important to reemphasize the impact of this disruption in the light of the present role of the NIMH training program in the growth of the mental health professions. The total operation of this program is today a major influence on the mental health fields. It is appropriate

to note that at the present time practically every medical school department of psychiatry has an NIMH training grant. Of those schools with an appropriate mental health specialization, almost all the major graduate departments of psychology, graduate schools of social work, and graduate schools of nursing have NIMH training grants. In most cases these include traineeships. In addition, other training centers, including many of the major psychiatric training hospitals, child guidance clinics and private, non-profit, psychiatric treatment centers as well as clinical psychology internship centers, provide training facilities and traineeships supported by NIMH funds. Grants are also provided to over 70 schools of nursing with basic collegiate programs for strengthening the psychiatric teaching for undergraduate nursing students.

In addition to providing needed financing for increasing the manpower pool, the NIMH training program has provided a means whereby the mental health professions have been able to implement the development of new program direction. Various policy statements over the years by our advisory committees have been translated into new training programs, which in turn have had their impact on trends in professional training.

Within the four core professions, the following is a brief summary of recent program developments.

In training programs in psychiatry, there have been a few new programs, with a continuing and increased emphasis on research training. Efforts are being made to stimulate and support research training of psychiatrists at all levels to increase the supply of competent research psychiatrists. The recommendations of the 1959 Florida conference on research training in psychiatry will provide a useful guide for further implementation of new program directions in research training. A larger number of qualified centers are prepared to offer training with this research emphasis.

In undergraduate teaching of psychiatry to medical students, the major new emphasis will be on human behavior. This area began very modestly in fiscal year 1960 with awards to four programs for a total of $125,000. Requests for new grants for review in January 1961 total about $800,000. It is apparent that there is much interest and potential for growth in this important area.

There were two conferences supported this year; one for the Professors of Psychiatry West of the Mississippi which was held at the University of Nebraska, and the Southern Professors of Psychiatry Conference held at New Orleans. These conferences have been reported to have had a stimulating effect on all phases of psychiatric teaching. The one held in New Orleans dealt with the problem of introducing the science of human behavior into the medical school curriculum.

In training programs in nursing, it is expected that this year it will be possible to support some of the new programs, none of which were awarded in fiscal year 1960. However, some expansion occurred in the continuing programs. In graduate education, a new doctoral program leading to the degree of Doctor of Nursing Science was fully established this year through the Psychiatric Nursing Department at Boston University. This program is designed to prepare clinical specialists for research, teaching, and high-level administrative positions in the field of mental health-psychiatric nursing. It is the second such doctoral program in nursing and sets somewhat of a precedent in doctoral education in nursing in that the focus is on clinical depth and research in nursing. The impetus and real support for this development was to a very considerable degree a consequence of NIMH training program efforts and in response to the critical need for a nucleus of well prepared nurses with clinical and research competence. In addition to this development in research training, there was more expansion in nursing in child psychiatry.

In undergraduate training the volume of applications for new grants for review in January 1961 totals about $500,000. This reflects the readiness for participation and contribution to the mental health field and the potential for actual growth in the field. Another development in undergraduate training was the awarding of a limited number of traineeships to selected general nursing students in the senior year at approved schools also offering graduate training in psychiatric nursing. These students must be interested in this graduate training upon completion of the baccalaureate degree.

A rather unique approach to short-term intensive training of non-psychiatric nursing faculty and key nursing service personnel was undertaken in the Western region this summer. This is a five-year project for which support was recommended in recognition of the urgent need for some special knowledge and skills in psychiatric nursing on the part of nursing faculty in other nursing areas, and most urgently as a vehicle for preparing non-psychiatric faculty members for the task of integrating psychiatric mental health content in curricula.

Two special projects have been completed and publications reporting the findings of each should be available by the end of 1960 or early in 1961. They are: (1) A project to study the problems and methods involved in incorporating needed aspects of social and psychiatric science into undergraduate nursing education, University of North Carolina School of Nursing; (2) A pilot project to design and evaluate a pre-service psychiatric aide training program, Wayne State University College of Nursing.

In training programs in psychology all programs are now on the procedure of advance notification of grant award. This was accomplished this last spring with the special allocation of $3,850,000, of which

$3,500,000 was used for grants in psychology and $350,000 was used for grants in public health mental health.

The broadened support in psychology, which was inaugurated in fiscal year 1959, now represents a sizeable proportion of the entire program. In fiscal year 1960, over $750,000 was awarded in psychology grants other than clinical psychology. The majority of these are in research training in such areas as child, physiological, social and experimental psychology. On a recent examination of the development in this area the Psychology Subcommittee noted that further expansion is necessary to help meet the needs for research personnel. However, since research training is already a basic responsibility of departments of psychology, grant support should be extended only to those meritorious programs which demonstrate their clear relevance to mental health.

Support for internship training in clinical psychology has been discussed in each of the past few years. Several staff surveys have elicited data of a conflicting nature as to the need for expansion of internship center support, the most desirable patterns of internship training, and the optimum type and amount of support by NIMH. It was felt that these questions need further consideration and plans are now underway to bring together a small group of leaders in the field of training in clinical psychology to discuss the above problems at length.

Senior Stipends, as a result of recent committe recommendation, will now be available for limited-term appointments of outstanding practicing clinical psychologists to university departments, and for exchange appointments between clinical settings and departments.

The undergraduate research stipends are apparently filling a definite need in the field and are expected to increase in size although remaining small in absolute amount of support.

In training programs in social work there has been an increase in scope of support with the addition of new categories of training activities in several fields of social work with relevance to mental health. For the first time (beginning July 1, 1960) teaching and traineeship funds have been provided for the fields of family and child welfare, corrections, aging and community planning. Additional program expansion was provided in the support of doctoral and third-year programs in social work. A new program was initiated for the purpose of recruiting social work students into mental health research careers. A special stipend, fixed at $600, will be awarded as a summer grant to first-year students in social work interested in obtaining supervised research experience during the intervening summer between the first and second years of training. Increased numbers of training centers have become interested in the possibility of broadened support and this has reflected itself in a large number of requests for support in juvenile delinquency, mental retardation, aging and alcoholism. In addition, a number of new doctoral programs have expressed an interest in developing research training activities at the post-master's and

postdoctoral levels. One university received a pilot project grant to explore differences in a variety of field experiences in connection with graduate social work education. Support was continued in a demonstration program providing for special preparation on a post-master's basis for community mental health services. A grant to the Council on Social Work Education supported a national conference on curriculum planning held this summer.

III. Future Objectives

It is quite clear that the present operation of the training program of the National Institute of Mental Health is a major resource for the mental health fields to obtain its share of the professional manpower pool. From the initiation of this training program in 1947 through fiscal year 1960, a total of over $100,000,000 has been awarded for training grants and almost 10,000 individuals have received one or more years of support for professional training in the mental health fields. An even greater number of persons have received indirect benefits by participating in the various training programs supported by these funds.

What is equally clear and compelling is that the program has not yet reached the level it can or should reach to provide a continued impetus for professional training in the mental health field. And it is not inappropriate to consider this need on a long-term basis over the next ten years.

In terms of sheer total need, and without spelling out the details of programmatic support, recent data re-emphasize the manpower problem in mental health for the future. The total professional manpower potential in the United States for the next decade will be the greatest in history. However, this increased supply of professional personnel will undoubtedly be the result of an even greater increase in demand and will be due to marked competition among all professional fields for trained personnel. At the same time, the increasing social demand for mental health services and the increasing awareness of the presence of emotional disorders will increase the urgent need for greater numbers of mental health personnel. The net result is that, without some continuous and strenuous efforts, the mental health fields will be in a losing competitive situation for the expected additional professional manpower in the next decade. The need is clear for both the personnel to provide the services and, with perhaps even greater urgency, the personnel to do the research which will eventuate in better knowledge and better services for mental health.

It is in this perspective that the role of a vigorous and expanding NIMH training program can continue to be a pivotal influence for the growing strength, in number and quality, of mental health personnel.

NATIONAL INSTITUTE OF MENTAL HEALTH
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Serial No. M-NP-MP-1*
1. Laboratory of Neurophysiology
2. Section on Membrane Physiology
3. Bethesda, Maryland and The Physiological Laboratory, Cambridge, England

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Electrical and Ionic Properties of Muscle Fibers.

Principal Investigators: W.H. Freygang, Jr. and R.H. Adrian

Other Investigators: None

Cooperating Units: The Physiological Laboratory, Cambridge, England.

Man Years:
Total: 1.8
Professional: 1.0
Other: .8

Patient Days: None

(Cambridge University contributed one additional man year. Dr. Adrian was a visiting scientist at the NIH in July and August).

Project Description:

Objectives: To determine the nature of the processes that control the transmembrane potential of muscle fibers.

Methods Employed: Electrical leads are inserted in a single living muscle fiber under conditions that make the transmembrane potential uniform over a length of one millimeter. The level of the transmembrane potential is controlled by means of electronic circuitry. Variations in the intracellular and extracellular ionic composition are achieved by bathing the muscle fiber in a number of special solutions. Estimates of the ease with which the normally present ions pass through the membrane at different transmembrane potentials are derived from the data.

Major Findings: In last years report it was noted that potassium ions meet greater resistance on their outward passage through the membrane as the driving force increases in this direction. Opposite effects are found for the

*Formerly No. M-NP-GN-9.

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Individual Project Report
Calendar Year 1960

Part A. (continued)

inward movement of potassium. The processes responsible for this phenomenon have been investigated and a time dependence has been noted. Moreover, these effects have current-voltage characteristics which make the contribution of the potassium concentration gradient to the total transmembrane potential an unstable time-dependent phenomenon.

Scientific Significance: These results can be employed to partially explain the puzzling oscillatory behavior of muscle membranes. Many of the results agree with the effects one might expect if a significant movement of potassium occurs in the internal tubular system of the muscle fiber. This is of interest since the network of the tubules is currently employed in order to explain the coupling between the electrical and mechanical activity of muscle. These interpretations are highly speculative, but nevertheless it seems likely that some process of this sort is operating.

Proposed Course of Project: Further work will be directed toward relating the electrical findings to the microstructure of muscle.

Part B included: Yes x No ___

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Calendar Year 1960

Part B. Honors, Awards, and Publications

Publications other than abstracts from this project:

None

Honors and Awards relating to this project:

Dr. Freygang has been invited to participate in a Symposium sponsored by the American Association for the Advancement of Science in New York City on December 26-28, 1960. This Symposium is cosponsored by the American Physiological Society and the Society of General Physiologists. It is entitled "Biophysics of Physiological and Pharmacological Actions". Dr. Freygang will present a paper entitled "Potassium Movement in Muscle-Anomalous Rectification".

Serial No. M-NP-MP-2
1. Laboratory of Neurophysiology
2. Section on Membrane Physiology
3. Bethesda, Maryland and The Physiological Laboratory, Cambridge, England

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Electrical and Ionic Properties of Muscle Fibers: Search for Special Membrane Properties in the I Bands of Muscle Fibers.

Principal Investigators: A. F. Huxley and W.H. Freygang, Jr.

Other Investigators:

Cooperating Units: The Physiological Laboratory, Cambridge, England

Man Years:
Total: .4
Professional: .2
Other: .2

Patient Days: None
(Cambridge University contributed 0.2 additional man year)

Project Description:

Objectives: To see if the portion of the muscle membrane over the I bands of muscle fibers has any special properties.

Methods Employed: A depolarizing current was passed through portions of the membrane until one was found at which a local contracture of the I band occurred. Differences in the membrane current during the passage of an action potential were measured in comparison with points on an A band at which a local contracture could not be elicited.

Major Findings: The analysis of the data has not been completed.

Scientific Significance: There are theoretical reasons that suggest that the areas of the I band that are sensitive to depolarizing currents might be electrically inexcitable or reflect the electrical activity of the tubular system.

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Proposed Course of Project: A statistical analysis of the data is underway.

Part B Included: Yes_____ No X .

Serial No. M-NP-LI-3
1. Laboratory of Neurophysiology
2. Section on Limbic Integration and Behavior
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Modification of the Lilly Primate Chair for the Squirrel Monkey (Saimiri sciureus).

Principal Investigator: Martha Carmichael

Other Investigator: Paul D. MacLean

Cooperating Units: None

Man Years: Patient Days: None

Total: 0.3
Professional: 0.1
Other: 0.2

Project Description:

Objectives: To construct a chair to restrain the squirrel monkey during brain stimulation studies involving the recording of the electroencephalogram, electrocardiogram, spirogram, and other measures of bodily function.

Methods Employed: See next heading.

Major Findings: Information pertinent to the construction of the chair was given in the progress report of 1958. For the publication of this description average measurements of the body and brain of this animal were obtained for presentation in the table shown below:

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Individual Project Report
Calendar Year 1960

Part A. (continued)

	NUMBER ANIMALS	MEAN	STANDARD DEVIATION
WEIGHT	76	717 gm.	± 170.4
BODY LENGTH	49	26 cm.	± 2.47
TAIL LENGTH	50	36 cm.	± 2.14
TOTAL LENGTH	48	63 cm.	± 3.57
HEAD LENGTH	45	5.4 cm.	± 0.21
HEAD WIDTH	45	4.1 cm.	± 0.36
BRAIN WEIGHT	21	26 gm.	± 1.72
BRAIN LENGTH	29	4.9 cm.	± 0.21
BRAIN WIDTH	30	3.5 cm.	± 0.17

Significance to Mental Health Research: Because of its small body and large brain the squirrel monkey is a desirable primate form for behavioral, neurophysiological, and neuroanatomical investigations. A New World monkey, it is readily available, relatively inexpensive, and easy to maintain. It lends itself to acute or chronic experiments involving brain stereotaxic techniques. A number of investigators, including some involved in space research, have consulted us about the use of the squirrel monkey and have obtained our design for the restraining chair.

Proposed Course of Project: Completed.

Part B included Yes X No ____

Serial No. M-NP-LI-3

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Individual Project Report
Calendar Year 1960

Part B: Honors, Awards, and Publications:

Publications other than abstracts from this project:

Carmichael, Martha and MacLean, Paul D. Use of squirrel monkey for brain research, with description of restraining chair. EEG Clin. Neurophysiol. (In press)

Serial No. M-NP-LI-4
1. Laboratory of Neurophysiology
2. Section on Limbic Integration and Behavior
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: An Investigation of the Relationship of the Visual Apparatus to the Limbic System II. Evoked Potential Studies

Principal Investigator: John A. Gergen

Other Investigators: Paul D. MacLean, Christopher Reynolds, and Donald Reis

Cooperating Units: None

Man Years: Patient Days: None

Total: 1.7
Professional: 0.9
Other: 0.8

Project Description:

Objectives: To investigate the possibility of visual afferents to the hippocampal formation. The source of afferents to the entorhinal area of the hippocampal gyrus is unknown. This area in turn possesses some of the major anatomical connections with the hippocampus. In cytoarchitectural studies of the entorhinal area, Cajal drew attention to a number of its similarities to the visual cortex and suggested the possibility of visual function.

Methods Employed: Squirrel monkeys are being used for this study because of the desirable size of their brains and because of their well-developed visual system. Both macro-electrode and micro-electrode techniques are being employed. A stimulating electrode is placed in the septum in order that an evoked response in the hippocampus of known source may be compared with one elicited by flash or by electrical stimulation at certain points within the visual system.

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Individual Project Report
Calendar Year 1960

Part A. (continued)

Major Findings: In the waking monkey we were unable to evoke potentials by photic stimulation that could be differentiated from background activity. We therefore explored the possibility that a detectable response might be more readily obtained in an animal anesthetised with chlorolose. In a series of twelve experiments performed under these conditions large evoked responses with latencies of 75 to 180 milliseconds were recorded in 8 of 12 preparations. The latency was usually 75 - 80 msec. Visual responses of shorter latency were also recorded from the entorhinal area. In subsequent experiments employing micro-electrodes it was shown that these large slow potentials may be accompanied by unit potentials. This finding, together with the observation that the large slow potential reverses polarity in the pyramidal layer of the hippocampus and interacts with responses evoked by septal stimulation, all attest that the visually evoked potentials are attributable to activity in the elements of the hippocampus and are not the result of volume conductor spread from the optic tract and lateral geniculate body. The earlier occurrence of the visually evoked response in the entorhinal area suggests that this area may relay the stimulus to the hippocampus.

Scientific Significance: This experiment was undertaken to obtain much needed information about the possible functional relationship of the visual system with the limbic system and its hippocampal formation. The findings reported here indicate that we have a promising type of experiment for exploring the relationship.

Part B. included Yes____ No X

Serial No. M-NP-LI-5
1. Laboratory of Neurophysiology
2. Section on Limbic Integration and Behavior
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Studies on the Functions of the Midline Nuclei of the Limbic System
I. Mammillary Bodies

Principal Investigator: Detlev Ploog

Other Investigators: Paul D. MacLean, Caroline Cobb, and Frauke Ploog

Cooperating Units: None

Man Years: Patient Days: None

Total: 1.6
Professional: 0.4
Other: 1.2

Project Description:

Objectives: The functions of several of the midline nuclei of the limbic system are obscure. Of these the mammillary bodies are of particular interest because phylogenetically they attain their greates size in man. Clinical evidence suggests that destructive lesions of these nuclei are associated with impairment of recent memory and other manifestations of Korsakoff's syndrome. About half of the fornix fibers from the hippocampus project to the mammillary bodies. Several years ago we found that propagated hippocampal seizures, which result in extensive disruption of function within the limbic system, abolish conditioned avoidance responses, as well as conditioned cardiac and respiratory responses. Because of the above-mentioned anatomical considerations disruption of function in the mammillary bodies was suspected to play an important part in the loss of the animal's capacity to perform these tests. The present experiments were therefore

Part A. (continued)

undertaken to learn whether or not ablation of the mammillary bodies would interfere with conditioned avoidance behavior.

Methods Employed: Squirrel monkeys were used for these studies. An avoidance test was devised which involved an alternate choice situation and also permitted the introduction of a delay to assess an animal's ability to perform a delayed response test. Seven animals were trained in the foregoing test and achieved a plateau performance of 80 to 100% correct trials in daily sessions of 20 trials. Two of these seven animals were able to perform at this level after the introduction of a one second delay. After an animal reached criterion lesions were placed in the region of the mammillary bodies by electrocoagulation. As an aid to stereotaxis, X-ray measurements of the skull were obtained prior to placing the electrodes. In our studies on cerebral localization of genital function it was learned that penile erection could be obtained by stimulating in the region of the mammillary bodies. This was an additional aid in the correct placement of the electrodes.

Major Findings: Five of seven animals survived for post-operative testing. In four of these the mammillary bodies were almost completely destroyed, and in the remaining animal the lesion involved only the medial part of the nuclei. Every animal (including two animals that performed the conditioned avoidance test with a one second delay) quickly regained its pre-operative level of performance in testing. In addition, there were no marked changes in general behavior.

Scientific Significance: The foregoing study offers fairly conclusive evidence that an animal's failur to perform conditioned avoidance responses during hippocampal seizures is not attributable to altered function of the mammillary bodies. The observations also throw some doubt on the role of the mammillary bodies in immediate recall functions. Our findings

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Individual Project Report
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Part A. (continued)

in another investigation (see Project Report, Serial No. M-NP-LI-6) and further substantiated in the present study, have shown that stimulation in parts of the mammillary bodies results in penile erection. This discovery, in addition to some other reported observations, suggests that these structures subserve functions related to the sexual behavior, and makes it obvious that further investigations of their functions should be planned accordingly.

Proposed Course of Project: To be continued.

Serial No. M-NP-LI-6
1. Laboratory of Neurophysiology
2. Section on Limbic Integration and Behavior
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Cerebral Localization of Genital Function

Principal Investigator: Paul D. MacLean

Other Investigators: Detlev Ploog, Sushil Dua, and Rollin Denniston

Cooperating Units: None

Man Years: Patient Days: None

Total: 2.9
Professional: 1.6
Other: 1.3

Project Description:

Objectives: The purpose of this study is to learn the cerebral localization of structures and pathways involved in penile erection. Detailed knowledge of the localization of this important sexual function would be valuable not only with respect to the phenomenon itself, but would also possibly lead to the identification of structures involved in related sexual manifestations and in social behavior conducive to the preservation of the species.

Methods Employed: Observations have been made on thirty-one male squirrel monkeys. Eighteen animals have been prepared for chronic study in order that exploration could be carried out under waking conditions. A special platform which is fixed to the animal's head allows one to apply the stereotaxic technique while the animal sits peaceably in a restraining chair. Electrodes are fixed at positive points so that further experimentation can be carried out. In the remaining thirteen animals observations have been made under acute conditions with the animal anesthetized and placed in a

Part A. (continued)

Horsley-Clarke apparatus. The loci of stimulation are determined by histological examination.

Major Findings: In last year's Progress Report we described the findings of positive loci in parts of the septum, the medial preoptic region, the region of the paraventricular nucleus, and along the course of the medial forebrain bundle. Since the last report it has been of great interest to discover that positive loci are also located in parts of the anterior thalamic group, in the medial part of the medial dorsal nucleus, and along the course of the mammillothalamic tract, including points impinging on the mammillary bodies.

We are currently exploring structures along the habenulolopeduncular tract and are also attempting to trace the pathways out of the diencephalon into the midbrain. Details of these investigations, together with findings related to ejaculation, will be given in next year's report.

Other Findings: In the septal, medial preoptic and medial anterior hypothalamic regions one may pass within a millimeter from a stimulation point giving erection and an apparent state of placidity to one giving rise to angry or fearful type of vocalization and the showing of fangs. Indeed, the mechanisms for these respective behaviors appear to be so close that when one passes through the transitional region one may obtain simultaneously both erection and a fearful-like or angry-like behavior. As one lowers the electrode a little deeper one may obtain only fearful or angry-like manifestations during stimulation, but see erection appear as a rebound phenomenon after stimulation is terminated. At points close to, or overlapping, those giving erection one may also elicit urination. Cardiac slowing, with or without irregularities and/or extrasystoles, may also occur. In a few instances the cardiac changes have persisted for several minutes after stimulat

Part A. (continued)

When one stimulates in the septum, anterior hypothalamus, or anterior thalamus, with intensities sufficient to elicit erection, seizure afterdischarges may commonly be recorded from the hippocampus. During these afterdischarges erections may become throbbing in character and reach maximum size. For several minutes afterwards one may see abnormal spiking activity in the hippocampus, and during this time erections may come and go for periods up to five minutes.

The determination of over 40 frequency-amperage curves has confirmed our original impression that the frequency and duration of the stimulating pulse are important factors in eliciting erection. Pulses of about 1 msec. and at a frequency of 20 - 30 per sec. are generally most effective for stimulation of the septal region and anterior thalamus, whereas very short pulses (10-50 μ sec.) and at a frequency of 60 - 100 per sec. appear to be optimum for stimulation in the medial forebrain bundle, subthalamus, and ventral tegmentum.

Scientific Significance: The findings in connection with the positive points in the ancient and medial part of the medial dorsal nucleus are of interest to consider from the standpoint of frontal lobotomy. In this operation an attempt is made to sever the connections between the medial dorsal nuclei and their related cortex in the orbitofrontal and prefrontal cortex. As is well-recognized this operation not infrequently has the unfortunate consequence of giving release to bizarre sexual behavior.

The findings pertaining to the mammillothalamic tract have interesting implications from the standpoint of phylogeny and the evolution of social structure in the mammal. This pathway is not found in the reptilian brain, but appears for the first time in the mammal and reaches its greatest size and development in man. Heretofore it has been alleged to be one of the silent areas of the brain.

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Individual Project Report
Calendar Year 1960

Part A. (continued)

The findings of the close relationship of mechanisms pertaining to penile erection and those involved in combative behavior would seem to be pertinent to the long recognized psychological and behavioral relationship of sexuality, aggression, and painful affects. One is reminded of two of Freud's observations in his monograph on the theory of sex: (1) "A number of persons report that they experienced the first signs of excitement in their genitals during fighting. . . ." and (2) ". . . The sexually exciting influence of some painful affects such as fear, shuddering, and horror is felt by a great many people throughout life and readily explains why so many seek opportunities to experience such sensations."

The findings pertaining to the hippocampus support our hypothesis that this structure participates in modifying the excitability of structures concerned with sexuality, as well as those involved in oral and combative functions.

Proposed Course of Project: To be continued.

Part B. included Yes X No ____

Serial No. M-NP-LI-6

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B. Honors, Awards and Publication:

Publications other than abstracts from this project:

1. MacLean, P.D., Ploog, D.W. and Robinson, B.W. Circulatory effects of limbic stimulation, with special reference to the male genital organ. Physiol. Rev., 1960, 40: 106-112.

2. MacLean, P.D. John F. Fulton (1899-1960). A Midsummer Reminiscence. Yale J. Biol. & Med. (In press)

Honors and awards relating to this project:

1. Invitation to Dr. MacLean to participate in the National Academy of Science Symposium entitled "Central Nervous System Control of Circulation", Washington, D.C., Nov. 1-3, 1959. Title of presentation: "The Limbic Structures and Their Connections with the Hypothalamus: Physiological Aspects".

2. Invitation to Dr. MacLean to discuss lecture by Dr. Lawrence Kubie entitled "How We Think", Meeting of Washington Psychiatric Association, Nov. 27, 1959.

3. Invitation to Dr. MacLean to give lecture entitled "A Neurophysiological Basis of Oral and Sexual Behavior" before the Department of Psychiatry and allied disciplines, University of North Carolina Chapel Hill, North Carolina, Feb. 20, 1960

4. Invitation to Dr. MacLean to organize a symposium entitled "Current Investigations on the Brain and Behavior" for the 97th Annual Meeting of the National Academy of Sciences, Washington, D.C., April 27, 1960, and to present a paper entitled "Localization of Genital Function in the Limbic System ("Visceral Brain").

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Individual Project Report
Calendar Year 1960

Part B. (continued)

5. Invitation to Dr. MacLean to discuss paper entitled "Organization of the Projections of the Anterior Group of Nuclei and Midline Nuclei of Thalamus to the Cingulate Gyrus, Hippocampal Rudiment and Septal Area in Monkey" by Paul I. Yakovlev et al, Meetings of the American Neurological Association, Boston, Mass., June 14, 1960.

6. Invitation to Dr. MacLean to give staff seminar at the Sheppard and Enoch Pratt Hospital, Oct. 8, 1960.

7. Invitation to Dr. MacLean to give lecture entitled "Cerebral Substrates of Sexual Function" as one of a series of lectures organized by the Interdisciplinary Program for Research in the Basic Sciences Related to Mental Health, University of California Medical Center, San Francisco, Nov. 15, 1960, and to present a number of seminars for this same interdisciplinary program.

8. Invitation to Dr. MacLean to give lecture entitled "A Neural Basis of Sexual Behavior" at the Langley Porter Neuropsychiatric Institute, San Francisco, Nov. 16, 1960.

Serial No. M-NP-LI-7
1. Laboratory of Neurophysiology
2. Section on Limbic Integration and Behavior
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Influence of Hippocampus on Excitability of Other Cerebral Structures.

Principal Investigator: John A. Gergen

Other Investigator: Paul D. MacLean

Cooperating Units: None

Man Years: Patient Days: None

Total: 1.2
Professional: 0.5
Other: 0.7

Project Description:

Objectives: In previous investigations we have reported prolonged behavioral changes following hippocampal seizures induced by electrical stimulation of the hippocampus itself or by stimulation of structures that are closely related to the hippocampus. A further illustration of such an effect is given in an accompanying project report (Serial No. M-NP-LI-6) entitled Cerebral Localization of Genital Function. The present investigation is attempting to gain insight into the nature of the neural alterations that lead to such prolonged behavioral changes.

Methods Employed: Squirrel monkeys are being used for these studies. A stereotaxic method is employed which allows one to perform cerebral stimulation and to record brain potentials while the animal sits quietly in a restraining chair. Observations are made on the effect of hippocampal afterdischarges on the recovery of its excitability, as well as the excitability of a number of subcortical structures.

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Individual Project Report
Calendar Year 1960

Part A. (continued)

Major Findings: Observations have been made on ten animals which have been observed for periods of one to six months.

The spontaneous hippocampal electroencephalographic activity differs from the rabbit and cat in that arousal results in only random, fast potentials of low voltage with no apparent rhythmic theta activity. In the waking animal it has not been possible to evoke potentials by auditory, visual, or somatic stimulation that can be differentiated from background activity.

Hippocampal seizures induced by stimulation of the hippocampus, fornix, septum, hypothalamus, and retrosplenial cortex have characteristic spike frequencies at 4 - 6, 9 - 11, and 18 - 22 per second. The usual seizure induced by direct hippocampal stimulation persists for 20 to 30 seconds, but can be prolonged to over 60 seconds by low frequency stimulation. There is evidence of poor propagation to the opposite hippocampus.

The early component of subcortical/peripherally evoked responses is unmodified by seizure activity, but the late response to click, flash and trigeminal nerve stimulation has been found to be suppressed during, although not immediately after, seizures.

At least three intrinsic hippocampal recovery cycles have been identified: (i) 10 to 30 sec. - recovery of electrically evoked responses and some spontaneous activity; (ii) 3 to 5 minutes - partial return of the capacity to sustain an electrically induced seizure; (iii) 20 to 30 minutes - constant reproducibility of the usual seizure. In some monkeys the findings have suggested that over 24 hours are required for full recovery.

Scientific Significance: A number of investigators have undertaken behavioral and endocrine studies involving direct or indirect stimulation of the hippocampus without making simultaneous electrical

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Part A. (continued)

recordings and without paying sufficient attention to the spacing and duration of stimulations. As demonstrated by the present investigation, a knowledge of the recovery of the excitability of the hippocampus would be basic to any investigation involving its stimulation directly or indirectly.

Proposed Course of Project: To be continued.

Part B. Included Yes X No

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Part B. Honors, Awards and Publications:

Publications other than abstracts from this project:

1. Stevens, J.R., Kim, C., and MacLean, P.D. Behavioral Effects of Chemical and Electrical Stimulation of Caudate Nucleus. A.M.A. Arch. Neurol. (In press)

Honors and awards relating to this project:

1. Invitation to Dr. Gergen to audit a conference on Computer Techniques in EEG Analysis, Brain Research Institute, University of California Medical Center, Oct. 29-30, 1960.

Serial No. M-NP-LI-8
1. Laboratory of Neurophysiology
2. Section on Limbic Integration and Behavior
3. Bethesda, Maryland

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Individual Project Report
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Part A.

Project Title: Individual and Social Behavior of Squirrel Monkeys (Saimiri scureus) in Captivity

Principal Investigator: Detlev Ploog

Other Investigators: Caroline Cobb, Frauke Ploog, and Paul D. MacLean

Cooperating Units: None

Man Years: Patient Days: None

Total: 1.2
Professional: 0.3
Other: 0.9

Project Description:

Objectives: For the purpose of interpreting the results of our brain stimulation experiments on the squirrel monkey it was desirable to be familiar with the individual and social behavior of these animals. We therefore undertook a study of a group of these animals and attempted to evaluate and quantify certain aspects of their behavior.

Methods Employed: The methods employed in this study were given in last year's Progress Report.

Major Findings: The major findings were given in last year's Progress Report and are now in the process of being incorporated in a paper for publication.

In the project report entitled Cerebral Localization of Genital Function (Serial No. M-NP-LI-7) attention was called to the finding of the close relationship in the brain of mechanisms involved in

Part A. (continued)

penile erection and in combative behavior. From this standpoint it is worthwhile to elaborate on findings from the behavioral study of the squirrel monkey that pertain to the question of sexuality and agression. Among the most interesting findings of this study were those revealing that penile erection may be displayed by male squirrel monkeys under a variety of conditions: (i) It may be performed by two strange animals at a distance, suggesting a form of greeting. A most effective way of eliciting this response is to hold up a mirror to the animal, presumably because the animal's own reflection serves as a kind of positive feedback. (ii) Erection may be displayed in the act of courting interest in the female. (iii) A dominant male may display erection to a subdominant male. It does so with thighs spread and the erect penis thrust almost up to the face of the submissive animal. The impression is gained that the submissive animal is expected to be quiet and reply in kind. If it does not, it may be viciously assaulted by the dominant male. The dominant male, Casper, in this colony, displayed to all of the other males, but none in turn displayed to him. In contrast, Edgar, the male lowest in rank, displayed to none of the other males, but all displayed to him.

The position that two monkeys assume during this display is somewhat comparable to that of two dogs mutually smelling the genitalia. It is to be remembered that the dog is dominated to a large extent by its olfactory sense, whereas the monkey is dominated by its visual sense. It would almost seem that one sees in the squirrel monkey a kind of "missing link" between the macrosmatic animal and the visually dominant animal.

Scientific Significance: In his monograph on the theory of sex Freud comments on the apparent desire of children to display their genitals and to see the genitals of others, and he concludes that this is a spontaneous sexual manifestation. He also comments on the cruelty component of the sexual impulse and its relation to the impulse to mastery. The

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Part A. (continued)

observations on the squirrel monkey make one wonder if penile display and the impulse to mastery are not inherently a part of the neural apparatus of the primate. The finding that the squirrel monkey assumes the same posture of penile display in courtship and aggression has special phylogenetic interest when it is recalled that the sexual posturing of some male birds is indistinguishable from their aggressive posturing. There are other considerations that lead one to wonder if the act of penile display in the monkey does not "generalize" to the eye so that the mere act of one animal's looking into the eyes of another becomes in itself an aggressive act. Monkeys seem in general to try to avoid looking each other in the eye, or, indeed, people in the eye. Is it possible that man with his superior intelligence has circumvented the tension of this awkward situation simply by assuming the loin cloth? In this connection it is interesting to recall that looking in the eye spells panic to some psychiatric patients, particularly some schizophrenic patients. On the contrary, the person who is well-adjusted finds it relatively easy to follow the half polite, half aggressive social dictum to look people "straight in the eye".

Proposed Course of Project: This project will be concluded with the publication of the findings.

Part B. Included Yes X No ____

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Part B. Honors, Awards and Publications

Honors and awards relating to this project:

1. Invitation to Dr. Ploog to give two presentations entitled "The Social and Sexual Behavior of Squirrel Monkeys" and "Some Implications of Ethology for Psychiatry" at the Addiction Research Center, U. S. Public Health Service Hospital, Lexington, Kentucky, June 21, 1960.

Serial No. M-NP-LI-9
1. Laboratory of Neurophysiology
2. Section on Limbic Integration and Behavior
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Preparation of a Stereotaxic Atlas of the Squirrel Monkey's Brain (Saimiri sciureus)

Principal Investigator: John A. Gergen

Other Investigators: Paul D. MacLean, George Creswell, and Martha Carmichael

Cooperating Units: None

Man Years: Patient Days: None

Total: 0.8
Professional: 0.3
Other: 0.5

Project Description:

Objectives: The squirrel monkey is a small New World primate which is not much heavier than the guinea pig, but which has a brain almost as large as the cat's. The animals used in this latoratory weigh on the average of 717 grams. The brain of this animal lends itself to stereotaxic and histological techniques. Because of these considerations and because it is easy to care for and requires relatively little space, we have found it a most desirable primate form for behavioral and neurophysiological studies in the N.I.H. setting. As no stereotaxic atlas of this animal's brain existed, we made our own atlas and since the previous report have continued to obtain X-ray, direct cranial, and brain measurements on animals used in various investigations in order to check on the accuracy of our atlas and to learn the amount of variation from one animal to another.

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Part A. (continued)

Methods Employed: The methods employed were outlined in last year's report. The only new addition has been the attempt to find a suitable embedding material that would not involve shrinkage of the brain.

Major Findings: Comparative measurements have been obtained on 37 brains. There are control X-ray measurements in 33 animals and careful fossa measurements with the skull in the Horsley-Clarke apparatus in 17 animals. We now have an extensive series of brains cut in the frontal plane in which the accuracy and quality of the sections are excellent. On the basis of this material the statement in last year's report can be repeated with greater assurance, namely: "Our findings to date suggest that one has a reasonable chance of placing an electrode within one millimeter of the desired structure."

We have not yet discovered a satisfactory method for embedding brains without shrinkage. We have devised an agar brain perfusion technique, however, which greatly facilitates the cutting and mounting of frozen sections and improves the quality of the sections.

Scientific Significance: In addition to providing essential information for our own studies, the preparation of this atlas will be useful to other laboratories. We have had several requests for such an atlas. In addition, the atlas will be valuable for obtaining comparative knowledge of the brain.

Proposed Course of Project: A line drawing atlas is currently being prepared that will permit inexpensive reproduction of a laboratory manual that can be circulated to other workers. A description of the agar brain perfusion technique for frozen sections will be submitted for publication.

Part B. Included Yes____ No X

Serial No. M-NP-LI-10
1. Laboratory of Neurophysiology
2. Section on Limbic Integration and Behavior
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Neuroanatomical Study of the Brain of the Hyrax

Principal Investigator: Paul D. MacLean

Other Investigators: John Gergen and George Creswell

Cooperating Units: None

Man Years: Patient Days: None

Total: 0.4
Professional: 0.1
Other: 0.3

Project Description:

Objectives: The hyrax (known familiarly as the cony or "rabbit of the rocks') is a small mammal about the size of a rabbit. It is found in eastern Mediterranean countries and in Africa. It is classed with the elephants and seacows under the superorder Paenungulata (Simpson, 1945).

Because of our interest in the functions of the mammillary bodies we were curious to learn whether or not this alleged relative of the elephant resembled it in being deficient in the mammillary bodies. The study of the behavior of an animal lacking a particular part of brain might give a clue as to the function of the structure in question. We therefore welcomed the opportunity to obtain a hyrax that died of a nematodal infestation in the Washington Zoo.

Major Findings: A brief description of the gross appearance of the hyrax brain was given in last year's report.

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Part A. (continued)

A search of the literature revealed a number of histological studies on the brain of the hyrax. Ibrahim and Shanklin (1941) and Jessup and Shanklin (1940) have, respectively, described the thalamus and the hypothalamus. Examination of serial sections of the brain of our specimen (Procavia) revealed no new findings. Far from being deficient, the mammillary body, mammillothalamic tract, and anterior thalamic nuclei are unusually well developed

According to Krabbe (1947) the pineal body of the hyrax (Procavia) never develops fully and must be considered as rudimentary. In this respect, at least, its brain would be similar to the elephant's. The pituitary gland is said to be somewhat more primitive than that of the elephant (Wislocki, 1940).

Other peculiarities of note are the small cerebellum and the well-developed auditory system as revealed by the large size of the lateral lemniscus, inferior colliculus, and medial geniculate (Taft, 1912).

Scientific Significance: From a taxonomic point of view it is of interest that the hyrax and elephant which are allegedly related to one another should have such disparity of development of the mammillary bodies and mammillothalamic pathways. In contrast to the elephant, which is deficient in these structures, the hyrax would provide an unusually well developed mammillo-thalamic-cingulate system for behavioral and neurophysiological studies in which such features were desired.

Proposed Course of Project: Concluded.

Part B. Included Yes____ No X

Serial No. M-NP-GN-8
1. Laboratory of Neurophysiology
2. General Neurophysiology
3. Bethesda, Maryland

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Individual Project Report
Calendar Year 1960

Part A.

Project Title: Measurement of pH changes in cerebral cortex.

Principal Investigators: S. Rapoport and W. H. Marshall

Other Investigators: A. Bak

Cooperating Units: None

Man Years:
Total: 1.2
Professional: .6
Other: .6

Patient Days: None

Project Description:

Objectives: To develop and test a glass electrode system for measuring pH of CNS tissue and to satisfactorily conduct these measurements in presence of other slow electrical potential changes in CNS.

Methods Employed: Using a glass membrane electrode (Nims type) which is proven to be not susceptable to Na+ and K+ ion changes and to follow pH changes faithfully. The system is direct reading and records pH with other pertinent data, such as spreading cortical depression.

Major Findings: None at this time.

Scientific Significance: These data are very important for general physiology of CNS ganglia.

Proposed Course of Project: Continue indefinitely depending on results obtained.

Part B. Included: Yes ___ No x

Serial No. M-NP-GN-23
1. Laboratory of Neurophysiology
2. General Neurophysiology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Electrophysiology of Hippocampal Neurons: Direct Stimulation of Hippocampal Pyramidal Cells, Firing Level and Membrane Time Constant.

Principal Investigators: E.R. Kandel and W. A. Spencer

Other Investigators: A. Bak and S. Lerner

Cooperating Units: None

Man Years:
Total: 2.8
Professional: 1
Other: 1.8

Patient Days: None

Project Description:

Objectives: To determine the membrane constants of hippocampal neurons.

Methods Employed: Cats were anesthetized with Evipal and decorticated. Hippocampus was directly exposed and stimulating electrodes were placed under direct vision on the fornix, for antidromic activation of pyramidal cells, and on the subiculum for orthodromic activation. In addition, a bridge circuit was used for passing current through the recording electrode in order to simultaneously stimulate and record from the impaled cell.

Major Findings: 1) The time constant of the hippocampal pyramidal cell membrane as measured with bridge unbalance and strength latency techniques is slightly less than 10 msec. 2) The resting total neuronal membrane resistance (with bridge unbalance technique) is 10 Megohms. 3). The specific transverse resistance is calculated to be approximately $1000 \Omega cm^2$ and the membrane capacitance is calculated to be 1 μF. These latter values are similar to those of motoneuron and suggests that both neural membranes are made of similar material. Since rheobasic

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Part A. (continued)

current is generally 3-5 x 10^{-10} Amps, one can calculate threshold depolarization knowing resting membrane resistance (10 Megohms). These calculations yield a threshold depolarization of 3-5 mV which compare favorably to the experimentally determined thresholds of 4-5 mV.

Scientific Significance: Analysis of membrane properties of cortical neurons.

Proposed Course of Project: Concluded.

Part B Included Yes x No ___

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Part B. Honors, Awards, and Publications

Publications other than abstracts from this project:

1. Electrophysiology of Hippocampal Neurons. III Firing Level and Time Constant. W.A. Spencer and E.R. Kandel

Other papers in this general program from M-NP-GN 20, 21, 22 of 1959 annual report are:

1. Electrophysiology of Hippocampal Neurons. I Sequential Invasion and Synaptic Organization. E.R. Kandel, W.A. Spencer and F.J. Brinley, Jr.

2. Electrophysiology of Hippocampal Neurons. II Afterpotential and Repetitive Firing. E.R. Kandel and W.A. Spencer

3. Electrophysiology of Hippocampal Neurons. IV Fast Prepotentials. W.A. Spencer and E.R. Kandel

All four of these papers have been accepted by the Journal of Neurophysiology and will appear May 1961.

Honors and awards relating to this project:

Dr. Alden Spencer was invited to present a seminar at the University of Minneapolis, April 8, 1960.

Dr. Eric Kandel was invited to present a seminar at the University of Indiana, April 19, 1960.

Drs. Kandel and Spencer have been invited to present some aspects at a symposium sponsored by the American Association for the Advancement of Science, December 30, 1960 in New York. The title of the symposium is Conference on "Current Problems in Electrobiology". Dr. Kandel will present a paper entitled: Electrophysiological Properties of an Archicortical Neuron.

Serial No. M-NP-GN-25
1. Laboratory of Neurophysiology
2. General Neurophysiology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Remote Microdrive for Unit Recording.

Principal Investigators: F. Strumwasser, J.J. Gilliam and A. Bak

Other Investigators: None

Cooperating Units: Instrument Engineering and Development Branch and Advance Research Associates

Man Years:
Total: .8
Professional: .5
Other: .3

Patient Days: None

Project Description:

Objectives: To devise a better mechanism to drive and control position of microelectrodes in anesthetized and chronic animal preparations.

Methods Employed: A small gear reduction system was designed and constructed by the Instrument Engineering and Development Branch. A small magnetic armature was mounted on the drive shaft which could be rotated by a two phase electric field system (Anderson and Laursen EEG & Clin. Neurophysiol., February 1958). In the current project the field coils were made very large so as to surround the preparation. The mechanical part mounted on the animal's head weighed only 7 grams.

Major Findings: Various technical difficulties were solved and the device operated satisfactorily.

Scientific Significance: Increased technical knowledge. Improved mechanical control of microelectrode in anesthetized and chronic preparations is a most important technical problem.

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Part A. (continued)

Proposed Course of Project: Further work will be directed toward adapting a miniature motor with field coils built into the assembly.

Part B Included: Yes ___ No x

Serial No. M-NP-GN-30
1. Laboratory of Neurophysiology
2. General Neurophysiology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Analysis of Mechanisms Involved in Sensory Discrimination: Thalamic Level.

Principal Investigators: B. Z. Renkin

Other Investigators: S. Lerner and A. Bak

Cooperating Units: None

Man Years:
Total: 1.8
Professional: .7
Other: 1.1

Patient Days: None

Project Description:

Objectives: Previous work with unitary recording technics has demonstrated a striking focusing effect of sensory response at cortical level. This was tentatively explained by inherent operation of partially shifted overlap and the excitability cycle. This work has been extended with control of anesthesia. With light anesthesia the detachable evoked reactions become so disorganized that pattern analysis was impossible (M-NP-GN-30, 1959). It was decided to explore the patterning of the reaction in the ventro basal complex of the thalamus using various anesthetics.

Methods Employed: It was found that Evipal was a satisfactory anesthetic producing less changes in the excitability cycle of the thalamic transfer process than other barbiturates. Under conditions in which cortical pattern identification was not possible, thalamic pattern remained consistent and susceptable to analysis.

Major Findings: The cortical pattern previously found under deep anesthesia for the cortex, but not demonstrable under light anesthesia, was found to be present at the thalamic level under light anesthesia. The data has not yet been fully processed.

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Part A. (continued)

Scientific Significance: This project will add to knowledge of sensory discrimination and perception.

Proposed Course of Project: Continue indefinitely.

Part B. Included: Yes X No ___

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Part B. Honors, Awards, and Publications

Publications other than abstracts from this project:

None.

Honors and awards relating to this project:

Dr. Renkin was awarded a National Science Foundation Fellowship to go to the Nobel Institute for Neurophysiology for the Academic Year September 1960 to September 1961 to work with Professor Ragnor Granit.

Serial No. M-NP-GN-31
1. Laboratory of Neurophysiology
2. General Neurophysiology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Direct Cortical Response

Principal Investigators: W. H. Marshall and S. Rapoport

Other Investigators: S. Lerner and A. Bak

Cooperating Units: Section on Physiology, Laboratory of Clinical Investigations

Man Years:
Total: 1.7
Professional: .5
Other: 1.2

Patient Days: None

Project Description:

Objectives: Study interactions of sensory projection and association areas of the brain as a function of: 1.) Activation of superficial layers of the cortex by electric shocks, 2.) Activity cycles as modified by sleeping, waking and alerting, and 3.) The correlation of short and long components of DCR and also long and slowly changing potential levels of transcortical potential

Methods Employed: Chronic preparations of cat and monkey are used with implanted electrodes.

Major Findings: Project is just getting underway. It has been found possible to maintain preparations several days with the dural membrane cut. The data obtained with relaxed drug preparations on activity cycle of DCR, mentioned by E.R. Kandel, W.A. Spencer and F.J. Brinley, Jr. in the American Journal of Physiology, 198, April 1960, has been confirmed and extended to very short intervals. Interaction between DCR in association area and auditory and visual stimulus has been explored in a preliminary way.

Scientific Significance: These observations are of fundamental importance in understanding operation of the brain.

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Proposed Course of Project: Continue indefinitely with modification as course of research suggests.

Part B Included: Yes_____ No X .

Serial No. M-NP-GN-32
1. Laboratory of Neurophysiology
2. General Neurophysiology
3. Bethesda, Maryland

NIH-PHS
Individual Project Report
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Part A.

Project Title: Data retriever for brief intervals (100 μsec).

Principal Investigator: A. Bak

Other Investigators: P. Carr

Cooperating Units: None

Man Years:
Total: 1.1
Professional: .3
Other: .8

Patient Days: None

Project Description:

Objectives: To develop an "on line" data retriever to enhance signal to noise ratio and to operate on time bits as small as 10.0 μsec.

Methods Employed: A fast vacuum tube switch has been developed which permits 10 μsec. bits of data to be sequentially stored and summed.

Major Findings: Final model yet complete.

Scientific Significance: Useful instrument for several pertinent problems.

Part B Included: Yes ___ No x

Serial No. M-NP-GN-33
1. Laboratory of Neurophysiology
2. General Neurophysiology
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: The Pyramidal Cell During Induced Hippocampal Seizure

Principal Investigators: E.R. Kandel and W. A. Spencer

Other Investigators: S. Lerner, A. Bak and D. Gaither

Cooperating Units: None

Man Years:
Total: 1.8
Professional: .6
Other: 1.2

Patient Days: None

Project Description:

Objectives: To study seizure mechanisms in pyramidal cells of hippocampus.

Methods Employed: Provision was made to initiate seizures by stimulation of fornix. Some preparations were made to insure absence of afferent fibers so that only collaterals were activated by antidromic stimulation. In nonfornix sectioned preparations seizure was induced by a combination of afferent barrage and recurrent collaterals. The potential changes of the dorsal surface of the hippocampus were recorded simultaneously with the intracellular records.

Major Findings: In the intact fornix preparation (seizure induced by afferent tetanus) seizures were induced immediately and were characterized by large abnormal membrane potential oscillations and abnormal spikes. Depolarization progressed to the point at which the cell could not fire thus terminating the seizure. The gross electrode record from surface recorded the characteristic waves of a seizure which were well synchronized with the intracellular membrane transients.

Seizure discharges in the deafferented fornix preparation were delayed until after cessation of tetanus. The

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spikes were "normal" and the cell membrane transients and spike discharges were not well synchronized with the gross electrode record from the surface of the hippocampus. Seizure in this case appears to be some kind of rebound phenomena.

Scientific Significance: These studies contribute to knowledge of normal and pathological physiology of the brain.

Proposed Course of Project: This project is concluded in present form. The general subject will be continued indefinitely.

Part B Included: Yes X No _____.

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Part B. Honors, Awards, and Publications

Publications other than abstracts from this project:

None

Honors and awards relating to this project:

Drs. Kandel and Spencer were invited to include this work in June, 1960, at a Symposium on "Basic Mechanisms in the Epileptic Discharge" conducted by the American EEG Society. This will be published in the first 1961 issue of Epilepsia.

Serial No. NIMH-NC-7
1. Neurochemistry
2. Physical Chemistry
3. Bethesda, Md.

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Individual Project Report
Calendar Year 1960

Part A.

Project Title: Investigations of Structures of some Proteins and Nucleic Acids

Principal Investigator: David R. Davies

Other Investigators: None

Man Years
Total: 1
Professional: 1
Other: 0

Project Description

Project: Investigations of the molecular configurations of some proteins and nucleic acids.

Objectives: a) To investigate the formation and structure of macromolecules related to ribonucleic acid. b) To investigate the crystallographic properties of some proteins in preparation for a major crystallographic investigation of their structures.

Methods Employed: a) X-ray diffraction studies of fibers of the synthetic polynucleotides. b) Growth of large single crystals of the proteins. X-ray diffraction investigations of their crystallographic properties.

Major Findings: a) The polynucleotide complex of polyinosinic and polycytidylic acid is known from previous work in this Section to give a diffraction pattern resembling that of natural ribonucleic acid. Further investigations have shown that it is possible to produce a crystalline form of this material. X-ray investigations have demonstrated that the structure of the crystalline form is very similar to that of deoxyribonucleic acid. In addition, it has been possible to transform the non-crystalline form into the crystalline form in the fiber. This evidence indicates that the structure of the natural ribonucleic acid is, in its ordered regions, two stranded in form with hydrogen bonded base pairs similar

Part A, continued:

to those in deoxyribonucleic acid. b) Large single crystals have been grown of the proteolytic enzymes, chymotrypsin and nagarse. An investigation of the properties of the nagarse shows that it is possible to proceed further into a detailed investigation of the molecular structure of this material.

Scientific Significance: a) Evidence has been accumulated for the structure of natural ribonucleic acid, a molecule believed to play a vital role in the phenotypic expression of the genotype. b) Through further detailed investigations of the structure of proteins a better understanding will be obtained of the basic mechanism for folding of these molecules. It is believed that this will lead to a relation between structure and junction at the molecular level.

Proposed Course of Project: Molecular model building and structure factor calculations to refine the structures of the synthetic polynucleotide structures. Preparation of heavy atom labeled compounds for further investigation of the structure of the nagarse.

Part B included Yes x

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Part B: Honors, Awards, and Publications

Publications other than abstracts from this project:

1. Kendrew, J. C., Dickerson, R. E., Strandberg, B. E., Hart, R. G. and Davies, D. R. Structure of myoglobin, Nature, 185: 422-427, 1960.

2. Davies, D. R. Polyinosinic plus polycytidylic acid: a crystalline polynucleotide complex, Nature, 186: 1030-1031, 1960.

3. Crick, F. H. C., Davies, D. R., Rich, A. and Watson, J. M. The molecular structure of polyadenylic acid, J. Mol. Biol. In Press.

Honors and Awards relating to this project:

Invited speaker at ACS Symposium on Metals in Biological Systems, New York, September 1960.

Invited speaker at Symposium on Ribonucleic Acid Structure at the First Annual Meeting of the British Biophysical Society, London, December 1960.

Serial No. NIMH-NC-10
1. Neurochemistry
2. Physical Chemistry
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Aggregation of Dyes Bound to Polyanions

Principal Investigator: Dan F. Bradley

Other Investigators: Audrey L. Stone, S. Geisser, M. Kenneth Wolf, Gary Felsenfeld, D. Neville

Cooperating Units: Section on Theoretical Statistics and Mathematics, NIMH; Harvard Medical School; Dept. of Biophysics, University of Pittsburgh

Man Years
Total: 3
Professional: 3
Other: 0

Project Description

Project: To investigate the aggregation of dyes bound to polyanions.

Objectives: There exist a large number of cationic dyes which exhibit striking metachromatic color changes when used to stain polyanions such as deoxyribonucleic acid, ribonucleic acid, heparin and hyaluronic acid in tissue sections. We have been developing from a broad experimental base a general theory to account for these color changes in terms of the interaction between pairs of dye molecules and the structure of the polyanions to which the dyes are bound.

Methods Employed: In order to control and measure the color changes more precisely we have been studying the absorption spectra of these metachromatic dyes bound to polyanions in solution rather than *in situ*. A striking fact about such bound dye molecules is that their color varies with the relative amounts of polyanion and dye. Quantitative measurement of this change permits the evaluation of the strength of interaction between neighboring bound dye molecules. It is the strength

Part A, continued:

of this interaction which determines the color seen by the histologist viewing stained tissue sections and is used by him to distinguish certain tissue components. Considerable effort is being devoted to development of the statistical theory which relates the experimental spectral data to the degree of dye-dye interaction, and a general treatment based on the theory of runs has been worked out in collaboration with Dr. S. Geisser.

Major Findings: Perhaps the single most important discovery is that the structure of a polyanion determines in part the strength of dye-dye interaction so that the color of bound dye can tell us about the polyanion to which it is bound. We have collected a considerable body of data which supports the generalization that the more rigid and well ordered the polyanion, the weaker the dye-dye interaction. For example, all samples of native, well ordered deoxyribonucleic acid (DNA) examined show the same low value of this interaction, but when they are disordered by heat denaturation, the strength of the interaction increases. This observation has been developed to the point where the color of bound dye can be used to determine the degree of nativeness of DNA specimens.

Applying this general principle to structural changes in synthetic nucleic acids it has been possible to confirm certain hypothesized transitions. A quantitative method of analysis in the microgram range for nucleic acids, mucopolysaccharides, and synthetic polyanions has been developed.

A detailed study of the interaction between dyes bound to plant, animal and synthetic acid polysaccharides has been completed. As a result of this work it is now possible to differentiate among them as well as to relate the observed differences in the staining properties of these polymers to the type of binding site, and their number and relative locations on the sugar moieties.

It has also been found that interactions between dyes bound to polymers occur with several dozen different polymers and dyes. The variation in the strength of the interaction for a given dye bound to a group of closely related compounds is greater for some dye-polymer combinations than others. Thus acridine orange is useful for examining structural differences in the polynucleotides

Part A, continued:

while methylene blue is more effective with the mucopolysaccharides.

Scientific Significance: As a result of these studies it is now possible to understand on a molecular basis how a dye like acridine orange is able to differentially stain RNA and DNA, living and dead cells, normal and tumor cells, etc. The use of the color of bound dyes to elucidate structural features of polymers of great biological importance is one of the most promising results of this program, and a result which was completely unexpected at the beginning. It is anticipated that further development along present lines will contribute to our understanding of the forces which hold planar molecules in particularly stable, stacked configurations as in the case of nucleotides in nucleic acids and of chlorophyll in chloroplasts.

Proposed Course of Project: Several studies are now in progress: 1) A detailed statistical-mechanical and quantum-mechanical study of the theory of dye-dye interaction. 2) An experimental and theoretical study of the cooperative effects between neighboring binding sites on a polymer. 3) A study of the peculiar nature of small length polymers or oligomers. Part of this work in conjunction with Drs. M. L. Lipsett and L. A. Heppel has already been published (Ref. 4) and a second article is in press (J. Biol. Chem.). 4) A study of the relation of the metachromasy of nerve membranes to the fixed-charge theory of the structure of the membrane. 5) A study of the relation of dye-dye interaction to the origin of cotton effects in bound dyes. 6) A study of the long range interactions between bound dyes that result in phenomena such as the photoactivation of nerves, inactivation of viruses, quenching of fluorescene, etc. 7) A study of the new and interesting class of copolymers in which a variable fraction of the sites are non-binding sites. Such polymers are particularly interesting because their physical and chemical properties may be varied continuously with the fraction of non-binding sites. 8) A study of the use of dye interactions in the elucidation of the molecular structure of the nerve-site agent, ganglioside. 9) Studies of the metachromasy of heparinoid compounds, particularly of the intermediate types, with a view toward application of the findings by histologists and pathologists. 10) Further exploration of interesting preliminary dye and optical rotatory observations which indicate a specific binding of histamine to heparin.

Part B included Yes x

PHS-NIH
Individual Project Report
Calendar year 1960

Part B: Honors, Awards, and Publications

Publications other than abstracts from this project:

1. Bradley, D. F. and Felsenfeld, G. Aggregation of an acridine dye on native and denatured deoxyribonucleates, Nature, 184, 1920-22, 1959.

2. Bradley, D. F. and Wolf, M. K. Neurochemistry of polynucleotides. Chapt. 7 in Neurochemistry of Nucleotides and Amino Acids. R. O. Brady and D. B. Tower, eds. New York, John Wiley, 1960.

3. Wolf, M. K. and Bradley, D. F. Quantitative dye spectroscopy with the aid of a semi-micro magnetic stirring bar, Stain Tech. 35, 44-45, 1960

4. Lipsett, M. L., Heppel, L. A. and Bradley, D. F. Complex formation between adenine oligonucleotides and polyuridylic acid. Biochim. Biophys. Acta, 41, 175-177, 1960.

Honors and Awards relating to this project:

Speaker: 138th annual meeting of the American Chemical Society, New York, 1960 (A. L. Stone)

Invited Colloquim Speaker (D.F.B.):
National Institute Arthritis and Metabolic Diseases, March 1960
National Academy of Sciences, June 1960
University of California Department of Chemistry, July 1960 and Nov. 1960
Lawrence Radiation Laboratory, Berkeley, Calif., July 1960
Institute of Muscle Research, Woods Hole, Aug. 1960
Purdue University, Nov. 1960
Polytechnic Institute of Brooklyn, Dec. 1960

Serial No. NIMH-NC-18
1. Neurochemistry
2. Physical Chemistry
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Enzyme Models

Principal Investigators: Sidney A. Bernhard, John Carter, Frances Kowitt, Yehiel Shalitin

Other Investigators: Ephraim Katchalski, Arieh Berger

Cooperating Unit: Department of Biophysics, Weizmann Institute

Man Years
Total: 3
Professional: 3
Other: 0

Project Description

Project: Synthesis and properties of enzyme models.

Objectives: To test detailed theories of enzymic catalysis by chemical synthesis of model compounds and studies of their catalytic and chemical properties. Ultimately, via such investigations, to synthesize a model enzyme.

Methods Employed: Since the variety of enzyme catalyzed reactions is enormous, it is necessary in any finite study to limit the models to either a particular enzyme or particular class of enzymes. In this investigation we have limited ourselves to the largest known class of enzymes with a common catalytic amino acid sequence. These are the series of enzymes catalyzing hydrolyses, esterifications, phosphate transfers and transpeptidations. All these enzymes have the common sequence -glycyl-aspartyl-seryl-glycyl-. The general method is then to synthesize organic and peptide models of this sequence. Through studies of the chemistry of these compounds and their derivatives, particularly via model building and chemical-kinetics a detailed chemical mechanism of the catalytic action may be derived.

Part A, continued:

Major Findings: The sequence -glycyl-aspartyl-seryl-glycyl- is catalytically inert. Derivatives of this sequence with the hydroxyl of serine esterified (a proposed enzyme-substrate intermediate) show no unusual, reactive chemical properties. Derivatives of this sequence in which the "beta" carboxyl group of aspartic acid is converted to an ester or an amide have striking properties. Thus for example, the beta benzyl ester derivative of this sequence is hydrolyzed (debenozylated) at a rate one million times faster than normal benzyl esters. The reaction has a "turnover rate" at neutral pH comparable with enzymatic reactions. Molecular model constructions have resulted in a theoretical proposal of the three dimensional conformation of this molecule in the course of reaction. This "intermediate" conformation has been proposed as the catalytically active form of the enzyme; the configuration being stabilized by the protein superstructure.

Careful kinetic studies have now been made of the dependence of the reactions of aspartyl-seryl peptide reactions on pH, temperature, optical rotatory conformation and secondary structure. It has been found that cyclization of the peptides occurs very rapidly in all cases, when the reactant is a β-ester in the aspartyl residue. Both cyclization and ring opening have been found to be $[OH^-]$ dependent.

The reactions of model asparagine compounds have been studied as well. N-carbobenzyloxy asparaginyl nitrophenyl ester has been found to be very rapidly cleaved to nitrophenol and N-carbobenzyloxy-asparaginyl imide. Further reaction occurs rapidly under mildly acidic conditions (pH 4-5) to yield products distinguishable by their optical rotatory properties. Since these are reactions which can occur in protein chains as well, the detailed nature of these cyclic rearrangements are under further investigation.

Scientific Significance: Represents a contribution to the specific stereochemical theory of biological processes. By understanding the influence of the detailed molecular structure on the chemical function of enzymes, it ultimately becomes possible to predict the effect of genetic or environmental aberrations of amino acids within a particular enzyme sequence - one of the major goals of biomedical research. In particular, amongst the list

Part A, Continued:

of enzymes with the active sequence (-glycyl-aspartyl-seryl-glycyl) is acetyl cholinesterase, the enzyme involved in neurological response.

Proposed Course of Project: To test the above proposed intermediate structure by trapping reactions. To investigate other potentially catalytic amino acid sequences.

Part B included Yes

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Individual Project Report
Calendar Year 1960

Part B: Honors, Awards, and Publications

Honors and Awards relating to this project:

Invited Speaker: (S.A.B.)

Rockefeller Institute, April 1960.
Cold Spring Harbor, Genetics Institute, April 1960.
Virus Laboratory, Univ. of Calif., Berkeley, July 1960.
Dept. of Chemistry, Univ. of Oregon, July, August 1960.
Medical School, Univ. of Oregon, August 1960.
American Chemical Society, New York City, September 1960.
Dept. of Chemistry, Howard Univ., October 1960.

Serial No. NIMH-NC-19
1. Neurochemistry
2. Physical Chemistry
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: A Theoretical Approach to the Problem of Sequence Determination in Proteins

Principal Investigators: S. Bernhard, D. Bradley, W. Duda

Other Investigators: None

Cooperating Units: International Business Machine Company

Man Years
Total: $1\frac{1}{2}$
Professional: $1\frac{1}{2}$
Other: 0

Project Description

Project: A theoretical approach to the problem of sequence determination in proteins.

Objectives: One of the most important concepts in molecular biology is that the function of a protein is determined by the sequence in which the component amino acids are linked together. Although this idea is widely held and is almost certainly correct, experimental evidence for it is only just beginning to accumulate. The major block to rapid development of this field is that the experimental determination of the amino acid sequence in even a single protein is an extremely difficult and laborious affair. To date, the sequences of only a few small proteins, (insulin, ribonuclease, ACTH) are known, although work is in progress on a large number of others.

Current experimental approaches to this problem in various laboratories are generally quite similar. Straightforward approaches such as the breaking off of amino acids from one end of the sequence and analyzing them singly are only feasible for short sequences of 5-10 amino acids. To solve the sequence of myoglobin with 153 amino acids it is first necessary to specifically fission the protein into small peptides and determine

Part A, continued:

the sequence in each of these small peptides. Then by use of enzymes which catalyze fissions at different points in the sequence, one obtains peptides which overlap the original peptides. From such data it is possible to piece together the sequence of the whole protein. Such a procedure may take 3-4 years work on the part of a rather large research team.

Now the choice of methods of protein fragmentation, average size of peptides, selection of peptides to be analyzed, and amount of sequence data to be obtained from each peptide as well as the method for using the data collected in reconstructing the overall sequence are all a matter of choice. We have been examining this problem from a logical-mathematical point of view in an effort to find an experimental design which will minimize experimental effort and an information processing system which will utilize experimental data optimally.

Methods Employed: At present, we are examining the problem from a theoretical viewpoint, using logical techniques and digital computers.

Major Findings: The first step in this project was to develop a logical system for processing bits of information about individual peptides to determine the unique sequence in the protein. Such a system has been developed in collaboration with Dr. W. L. Duda at the IBM Company. We have provisionally named this system the Logical Unique-Sequence Tracer and have used it to reconstruct long sequences (100 amino acids) from what seemed to be a hopeless confusion of data. However, the system cannot be used to its maximum efficiency by an individual because it involves a very large number of logical decisions so that it is being programmed for a high speed digital computer. With this program in operation, sequencing can be done with a minimum of experimental data.

It is planned to carry out gedanken fission experiments to find out on a statistical basis for real proteins how much information value is contained in various-sized peptides, the optimum size of peptides, value of determining only partial sequences on peptides, etc.

A preliminary result of great interest is that a method of "indifferent" fission in which a relatively large number of peptide bonds are broken with about equal

Part A, continued:

velocities, e.g. by acid hydrolysis, is suggested as a method which might provide the optimum distribution of breaks in the protein to achieve maximum information. We hope to test this suggestion experimentally in conjunction with scientists in England who are working on the sequence of myoglobin.

The method of logical sequencing of composition data has now been translated into a "computer decision methodology." This involves two distinct and consecutive processes. (1) The sorting out of information into distinct peptides in respect to each (of the 20) amino acid; and (2) the logical overlapping of the distinct peptides. The former process has been found to be the more difficult to handle. The results thus far indicate; (A) that the computer can solve the problem of linear sequence given sufficient compositional data on peptide fragments; (B) that although the amount of information required for total sequence is less than was anticipated, important reduction in data required can be achieved by relatively minor allowances of restricted uncertainty; (C) that errors arising from either the inability to distinguish two similar amino acids or to exactly determine the integral number of a frequently recurrent amino acid do not introduce the requirement for large increases in data.

Scientific Significance: It is anticipated that this work will contribute materially to progress in the sequencing of proteins. This is a focal point of biological research today for not only is the sequence intimately involved with the function of enzymes, but it is almost certain that amino acid sequences on proteins are determined by sequences of nucleotides in the genetic material deoxyribonucleic acid. This work is therefore intimately involved with the fundamental problem of how genetic information in the gene is translated into action in the cell.

Proposed Course of Project: The Logical Unique-Sequence Tracer system will be programmed for the IBM 709 computer and a number of gedanken experiments will be performed with the system. After we have obtained a sufficient background of experience using the method, we intend to apply it to the problem of the sequence determination of myoglobin, and if successful, on other proteins.

Part B included Yes

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B: Honors, Awards, and Publications

Honors and Awards relating to this project:

Invited Speaker: Second Symposium on Mathematical Methods in Biology, I.B.M., Endicott, New York, September 1960 (S.A.B. and W.L.D.)

Serial No. NIMH-NC-20
1. Neurochemistry
2. Physical Chemistry
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Inter-relationships between Amino Acid Composition and sequence, molecular structure and Biological Function

Principal Investigators: S. Bernhard, M. Gellert, and D. Neville

Other Investigators: T. Viswanatha, E. Charney, NIAMD, Maurice Fox.

Cooperating Units: Laboratories of Pharmacology and Toxicology and Physical Biology, NIAMD; Rockefeller Inst. for Medical Research

Man Years
Total: 2.5
Professional: 2.5
Other: 0

Project Description

Project: To produce and investigate natural variants of a proteolytic enzyme.

Objectives: In order to examine the enzymatic mechanism and substrate specificity of enzymes, it would be extremely valuable to have available different forms of the enzyme having altered catalytic properties and specificity. By selecting for mutant forms of a bacterial enzyme, it is hoped that a large number of such variants can be produced.

Methods Employed: Various strains of Bacillus subtilis produce an extracellular proteolytic enzyme (subtilisin). It is possible to culture the cells under conditions where function of this enzyme is essential for growth, i.e. an essential growth factor is tied up in a substrate of the enzyme. By tailor-making substrates which are poorly hydrolyzed by the normal enzyme, we plan to select for mutants making enzyme of altered specificity. This altered specificity will then be correlated with the amino-acid sequence and the physico-chemical properties of the enzyme.

The physical and chemical properties of the enzyme, and in particular the site of enzymatic activity, are being

Part A, continued:

investigated by kinetic, spectrophotometric and optical rotary dispersion methods.

Major Findings, Scientific Significance and Proposed Course: A tryptophan-requiring mutant of B. subtilis strain 163 has been obtained. It has been shown that this strain grows poorly with certain tryptophan-requiring peptides as its sole source of tryptophan.

Experiments are now in progress to determine under what conditions this strain produces subtilisin, and hence what conditions are suitable for mutant selection.

The secondary and tertiary structure of the enzyme has been investigated in relation to enzymatic activity. The enzyme chain has been found to be devoid of covalently bridged links (S-S bridges); the molecule being held together in a specific active configuration to a large extent by interactions between hydrocarbons. The significance of this type of interaction in determining biological activity and molecular geometry has been studied by observing the changes in spectra and in the optical rotary dispersion, of the non-polar chromophores tyrosine and tryptophan, both in the active and heat-inactivated enzyme, and in free solution. In the active configuration, at least some of these chromaphores are aligned relative to the peptide structure and/or to each other, and are inaccessable to the solvent. Although anomalous rotatory dispersion in the absorption band of the chromophores has long been predicted for such a situation, it has been experimentally verified for the first time. The enzyme site is accessible to the solvent medium, and the solvent medium affects catalysis under conditions such that the molecular geometry of the protein remains invariant. It would appear from these results, that non-polar forces in the interior of the enzyme molecule are at least partially responsible for determining the specific geometry of the enzyme site.

By means of specific radioactive labeling of the active site with a P^{32} containing organo-phosphate inhibitor, and partial degradation of the enzyme, an 8 amino acid fragment has been isolated containing 50% of the radioactive label. This result presents a method of chemically screening mutant enzymes for changes in amino acid composition in the region of the active site. Similarly to many organo-phosphate reactive enzymes, this fragment

Part A, continued:

investigated by kinetic, spectrophotometric and optical rotary dispersion methods.

Major Findings, Scientific Significance and Proposed Course: A tryptophan-requiring mutant of B. subtilis strain 163 has been obtained. It has been shown that this strain grows poorly with certain tryptophan-requiring peptides as its sole source of tryptophan.

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Part A, continued:

contains the amino acids, glycine, aspartic acid, serine-P^{32} and proline.

Part B included No x

Serial No. M - CP 1
1. Lab. of Cellular Pharmacology
2.
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: The Mechanism of Action of the Methionine Activating Enzyme

Principal Investigators: S. Harvey Mudd, M. D.

Cooperating Units: None

Man Years:
Total: 1-5/6
Professional: 2/3
Other: 1-1/6

Project Description:

Objectives:

Mammals, plants and fungi and bacteria utilize the methyl group of methionine for biological methylations. As a result of recent work on the mechanism of transmethylation reactions, it has been established that in reality activation of methionine is a prerequisite to the transfer of its methyl group. Biologically the activation reaction is catalyzed by an enzyme which converts methionine to S-adenosylmethionine. In this reaction, adenosine triphosphate plays an essential role; specifically adenosine triphosphate fulfills a dual function inasmuch as it serves a) directly or indirectly as a donor source of its adenosine moiety, which is incorporated in "active methionine", and b) as an energy source, since it has been calculated that the methylsulfonium bond in "active methionine" is roughly equivalent to the pyrophosphate bond in adenosine triphosphate.

Results of detailed studies with enzymes isolated from mammalian liver, yeast and E. coli indicate a similar type of mechanism for this reaction. The terminal phosphate of adenosine triphosphate is liberated as inorganic phosphate while the two proximal phosphates are

freed as inorganic pyrophosphate. These and other experiments now in the literature indicate that a puzzling new chemical mechanism is at work here, and further work seems justified to aid in understanding this reaction.

Major Findings:

Broadly speaking at the point where this work stood a year ago one could envision two types of mechanisms by which the methionine activating enzyme works. These mechanisms are rather unusual and therefore interesting as illustrating new types of enzymological processes. The possibilities are most easily visualized by stating that it appears that the first step in the overall reaction may be the removal of the terminal phosphate of ATP without obtaining as a product the expected ADP. To do this (a) the ADP may become "enzyme bound" (b) the terminal phosphate may migrate intramolecularly to form a "phospho-ADP".

To explore possibility (a), highly radioactive ATP was incubated with enzyme in the absence of methionine. The protein was subsequently separated from all small molecular weight material by gel filtration, a newly available, extremely rapid, gentle, and efficient method. The results indicate that enzyme-bound ADP is not formed. An interesting side finding resulted however, with the discovery that the product, S-adenosylmethionine, is bound tightly and specifically to the enzyme. This opens to exploration a series of interesting questions (1) what is the chemical basis and nature of the binding (2) what changes does the binding cause in the physical and chemical properties of the enzyme (3) what changes occur in the chemistry of the S-adenosylmethionine as a result of binding (4) can this be used as a means of labelling the active site of the enzyme preparatory to study of the constitution of this active site (5) will the enzyme-product complex have properties sufficiently different from the enzyme to allow further purification of the enzyme on this basis (6) can the active sites of the enzyme be "titrated" by determining maximum binding capacity. It is hoped to investigate these questions in the future.

In regard to possibility (b), it has been attempted to obtain the hitherto unknown "phospho-ADP" compounds for direct testing. A variety of these are theoretically possible. To date 2'-phospho-ADP and 3'-phospho-ADP

have been tested and found inactive. Work is now proceeding on the synthesis of a 6-phosphoamino derivative which is considered to be the most likely intermediate. It is planned to continue this synthetic work as the most practical approach to the solution of the long-standing problem of the mechanism of action of the methionine activating enzyme.

Scientific Significance:

The significance of understanding methionine activation was discussed above. Apart from this, study of the enzyme-product binding system is significant in offering an unusual sort of model of a highly specific and quite irreversible interaction between a protein and a small molecular weight material, a model which has some analogies to a great variety of biologically important situations, all the way from antigen-antibody complexes to neuro-receptor-chemical effector interactions.

Proposed Course of Research:

Part B included Yes X No _____

Cantoni, G. L., Methionine Activating Enzyme. Chapter in: Biochemist's Handbook, Cyril Long, ed. E. and F. N. Spon.

Serial No. M - CP 3
1. Lab. of Cellular Pharmacology
2.
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Studies on the Enzymatic Synthesis of Methionine by Transmethylation from Betaine or Dimethylthetin

Principal Investigator: Werner A. Klee, Ph. D.

Other Investigators: Giulio L. Cantoni, M. D.

Cooperating Units: None

Man Years:
Total: 1-2/3
Professional: 3/3
Other: 2/3

Project Description:

Objectives:

To study the interrelationships among the enzymes of liver which are concerned with the transfer of alkyl groups from "onium" compounds to homocysteine.

Methods Employed:

Major Findings:

The enzyme betaine-homocysteine methylpherase which catalyzes the biosynthesis of methionine from betaine and homocysteine has been discovered in the livers of rat and the horse. It is presumably present in other mammalian livers.

This enzyme is different from the enzyme thetin-homocysteine methylpherase which catalyzes a similar reaction and which has been extensively studied in this laboratory. (See CP 18.) The two enzymes have been compared with regard to their physicochemical properties, intracellular distribution, and developmental characteristics as revealed in studies of

neonatal and regenerating livers.

Scientific Significance:

The fact that this enzyme preparation is able to utilize betaine, which is naturally occurring, much more efficiently relative to other methyl donors, which are not known to occur in mammals, than other enzyme preparations studied in this laboratory suggests that this enzyme may be the most important physiological catalyst of methionine synthesis by transmethylation. The highly purified THMPase studied in this laboratory may play some other, very different, physiological role.

Proposed Course of Research:

Part B included Yes _____ No X

Serial No. M - CP 6
1. Lab. of Cellular Pharmacology
2.
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: The Conversion of Phenylalanine to Tyrosine

Principal Investigator: Seymour Kaufman, Ph. D.

Other Investigators: None

Cooperating Units: None

Man Years:
Total: 1
Professional: 1/3
Other: 2/3

Project Description:

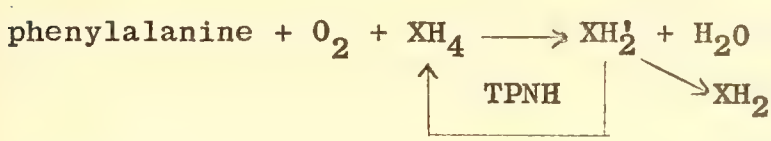
Objectives:

The oxidation of foodstuffs, which ultimately supplies the energy for all cellular functions, can be effected by two completely different processes. Organic compounds can either be oxidized by dehydrogenation, the removal of hydrogen, or by oxygenation, the addition of oxygen to the substrate molecule. The first type of reaction predominates in carbohydrate and fat metabolism. The mechanism of this kind of oxidation has been the subject of investigation for 50 years and is now quite well understood. Oxygenation reactions are encountered mainly in the cellular catabolism of ring compounds such as aromatic and heterocyclic amino acids, hormones and drugs. In contrast to dehydrogenations, the mechanism of oxygenation reactions has remained obscure. The conversion of phenylalanine to tyrosine is an oxidation reaction of this type and the goal of this study is to gain insight into the mechanism of this kind of oxidation reaction.

Part A.

Major Findings:

Previous work on the mechanism of the reaction established the following general scheme:



XH_2 had been identified as the 7,8-dihydropteridine but the structure of XH_2', the pteridine-intermediate, had not been determined. The intermediate has now been prepared chemically by oxidation of the tetrahydropteridine (XH_4) with 2,6-dichlorophenol-indophenol. The synthesized compound has all the expected properties of the intermediate which is formed enzymatically during the conversion of phenylalanine to tyrosine. As predicted by the above scheme, it is a very labile compound, breaking down even in the frozen state to the inactive 7,8-dihydropteridine. This lability has precluded structural studies by the usual methods of chemical analysis. Evidence has been obtained, however, which indicates that the active compound is the 5,6-dihydropteridine, a tautomeric form of the inactive compound.

Scientific Significance:

With the identification of the XH_2' pteridine which is the primary product of the tetrahydropteridine, the overall reaction catalyzed by the rat and sheep liver enzymes can be written in chemical terms. It is now clear that the sheep liver enzyme catalyzes a reaction which is quite similar to that of an enzyme which has already been described, i.e., dihydrofolic reductase. The sheep liver enzyme can be named 5,6-dihydropteridine-reductase. Considering the known specificity of enzymes, along with the fact that the sheep liver enzyme can function with the natural cofactor, it seems likely that the latter compound, as isolated from liver, is in the 5,6-dihydro form. It can also be predicted that this form of the natural cofactor must be stabilized in some unknown structural manner to retard the breakdown to the inactive 7,8-dihydro form.

Part A.

Proposed Course of Research:

Studies on the oxygen-activation step will be started. Studies will also be carried out with the natural cofactor to see if the overall mechanism which has been elucidated with the use of synthetic tetrahydropteridines, also applies with the natural cofactor.

Part B included Yes X No _____

Part B.

Kaufman, S., The participation of tetrahydrofolic acid in the enzymic conversion of phenylalanine to tyrosine. Biochim. Biophys. Acta, 1958, 27: 428.

Kaufman, S. Studies on the mechanism of the enzymatic conversion of phenylalanine to tyrosine. J. Biol. Chem., 1959, 234: 2677.

Serial No. M - CP 8
1. Lab. of Cellular Pharmacology
2.
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Studies on the Cofactor Required for the Enzymatic Conversion of Phenylalanine to Tyrosine

Principal Investigator: Seymour Kaufman, Ph.D.

Other Investigators: None

Cooperating Units:

Man Years:
Total: 1-1/3
Professional: 1/3
Other: 3/3

Project Description:)
) See Project M - CP 6
Objectives:)

Methods Employed:

Standard methods of fractionation of organic compounds.

Major Findings:

The attempts to improve the isolation procedure for the cofactor are continuing. A new source of the material, i.e., chicken liver, is being explored as a potential large-scale source. It has been found that the activity can be adsorbed onto charcoal from boiled extracts of liver. The active material can be eluted in moderately good yield. This step may provide a suitable first step in the isolation procedure.

It has been found that aged preparations of purified cofactor which have lost considerable activity can be partially reactivated by hydrogenation over a palladium catalyst. This finding is consistent with the postulated pteridine structure for the cofactor.

Scientific Significance:

The finding that pteridines such as tetrahydrofolic acid can function in an oxidation-reduction reaction raises the possibility that this class of compound may play a considerably wider role in intermediary metabolism than has been suspected up to now.

Proposed Course of Research:

The purification and the studies of the structure of the cofactor will be continued.

Part B included Yes X No ____

Kaufman, S., and Levenberg, B. Further studies on the phenylalanine-hydroxylation cofactor. J. Biol. Chem., 1959, 234: 2683.

Kaufman, S. The nature of the primary oxidation product formed from tetrahydropteridines during phenylalanine hydroxylation. J. Biol. Chem. (In press.)

Serial No. M - CP 9
1. Lab. of Cellular Pharmacology
2.
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Clinical Studies on Phenylketonuria

Principal Investigator: Seymour Kaufman, Ph.D.

Other Investigators: Peter Weiss, M. D.

Cooperating Units: None

Man Years:
Total: 1-1/3
Professional: 1/3
Other: 3/3

Project Description:

Objectives:

Biochemically, the disease phenylketonuria, is characterized by the abnormal excretion of phenylalanine and metabolites derived from it. For the most of these metabolites, such as phenylpyruvate, the pathway of their formation from phenylalanine is fairly well understood. For the excretion product, o-hydroxyphenylacetate, however, little is known about its metabolism except that it is derived from phenylalanine. The object of this investigation was to study the metabolism of o-hydroxyphenylacetate. A more immediate goal was to determine whether glutamate or phenylpyruvate was the more direct precursor of the hydroxyphenylacetate in the phenylketonuric.

Methods Employed:

Paper chromatography and chemical determinations.

Major Findings:

A sensitive micro method for the determination of o-hydroxyphenylacetate in urine, based on the chromatographic separation from interferring substances, has been

developed. Using this technique, the high rate of excretion of the compound in a phenylketonuric child has been confirmed. The feeding of glutamate did not result in the excretion of hydroxyphenylacetate in a patient with the disease.

Scientific Significance:

Because of the negative nature of the results, the source of hydroxyphenylacetate in these patients remains to be elucidated.

Proposed Course of Research:

The project has been completed.

Part B included Yes ____ No X

Serial No. M - CP 10
1. Lab. of Cellular Pharmacology
2.
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Biosynthesis of Norepinephrine

Principal Investigators: Ephraim Levin, M. D.
William F. Bridgers, M. D.
Seymour Kaufman, Ph. D.

Other Investigators: None

Cooperating Units: None

Man Years:
Total: 1
Professional: 1/3
Other: 2/3

Project Description:

Objectives:

This investigation is concerned with the mode of biosynthesis of the suprarenal hormone norepinephrine. Evidence from tracer studies has indicated that one route of biosynthesis of this substance is via hydroxylation of hydroxytyramine (DOPamine). A study is being made of the cofactor requirements and enzymatic mechanisms of this reaction, both as the route of formation of an important hormone and probable neurohumoral agent, and as a possibly typical biological non aromatic hydroxylation.

Methods Employed:

The enzyme involved has been purified by the procedures of classical enzymology to a point where it is now possible to measure its activity by the very sensitive and accurate standard fluorimetric techniques for norepinephrine and epinephrine.

Part A.

Major Findings:

The enzyme which catalyzes the hydroxylation of DOPamine to form norepinephrine has been further purified. It has been found that ascorbic acid and fumaric acid markedly stimulate the reaction, although the exact roles played by these factors has not been completely elucidated. In a study of substrate specificity, it has been found that phenylethylamine, p-tyramine, and epinine are also hydroxylated. The product formed by the hydroxylation of epinine has been identified as epinephrine.

Scientific Significance:

Surprisingly little has been established regarding the enzymatic mechanisms which the body employs in the biogenesis of the catechol amines. It is hoped that information gained from this investigation will shed some light both on the formation of these hormones and on the general mechanism of biological hydroxylation.

Proposed Course of Research:

Further purification of the enzyme is planned, followed by a study of the details of the reaction mechanism.

Part B included Yes X No _____

Part B:

Levin, E. Y., Levenberg, B., and Kaufman, S. The enzymatic conversion of 3,4-dihydroxyphenylethylamine to norepinephrine. J. Biol. Chem., 1960, 235: 2080-86.

Levin, E. Y., Levenberg, B., and Kaufman, S. Conversion of DOPamine to norepinephrine catalyzed by a soluble enzyme system. Federation Proceedings, Vol. 18, No. 1, March, 1959.

Serial No. M - CP 14
1. Lab. of Cellular Pharmacology
2.
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Studies on the Mechanisms and Pathways of Amino Acid Incorporation Into Protein

Principal Investigator: G. L. Cantoni, M. D.

Other Investigators: H. Gelboin, S. Luborsky, W. Klee, Maxine Singer,* Claude Blanc

Cooperating Units: None

Man Years:
Total: 1-1/3
Professional: 2/3
Other: 2/3

Project Description:

Objectives:

Proteins are known to be composed of amino acids linked through peptide bonds in a sequence which is specific and unique for each protein and for different species and tissue. In broad terms it has been generally assumed that genetic information is stored in the cellular DNA and somehow transmitted to RNA which, in an equally unknown fashion, specifies the sequence required for synthesis of a particular protein.

Although an obligatory relationship between RNA and protein synthesis has been postulated for several years this relationship has remained essentially undocumented until a few years ago when it was discovered that cytoplasmic RNA (called S-RNA) plays a role in the activation of amino acids and in the transfer of the activated amino acids to microsomes, where protein synthesis takes place.

*Laboratory of Biochemistry and Metabolism, NIAMD

Part A.

The present status of the problem is schematically represented in equations:

1a) $\text{amino acid} + \text{ATP} \xrightleftharpoons{\text{Enzyme 1}} \text{Amino acid-AMP-E,} + \text{PP}$

1b) $\text{amino acid - AMP-E,} + \text{SRNA} \xrightleftharpoons{\text{Enzyme 1}} \text{S-RNA-AA} + \text{AMP} + \text{Enzyme 1}$

2) $\text{SRNA-AA} + \text{Ms} \xrightarrow{\text{Enzyme System 2}} \text{Ms-AA} + \text{(SRNA)}$

3) $\text{Ms - AA} \xrightarrow{\text{Enzyme System 3}} \text{Protein}$

With reference to steps 1a and 1b it has become clear that there are specific activating enzymes for different amino acids and possibly that there are as many activating enzymes as there are amino acids in protein. It has also been established that S-RNA exhibit specificity for different amino acids, although the basis for this specificity is unknown. Furthermore, it has been established that a single protein catalyzes both steps.

With regard to step 2, much less is known due to the greater complexity of the system and to the fact that the microsomal structure is insoluble and defies fractionation by the standard techniques. It has been found, however, that more than one enzyme is required and in addition that GTP and ATP are necessary for the transfer. There is some evidence from work of this laboratory that the amino acid is transferred to microsomal ribonucleic acid prior to incorporation in a peptide bond but the details of the transfer are quite obscure.

As to step 3, the conversion of a microsomal bound polypeptide to a free protein, essentially nothing is known about it and it is estimated that more than one enzyme will be found necessary.

Part A.

It will be apparent, if the above scheme is correct at least in the main outline, that S-RNA plays a key and dual role in the process of protein synthesis in that it must "recognize" the activated amino acid then transfer it to the microsomal system. The objective of this and related projects has been to investigate, in as much detail as possible, steps 1 and 2 and in particular to concentrate on the biological role of S-RNA in the hope of deriving a clue to principles of biological coding mechanisms.

Major Findings:

Purification procedures have been developed to allow partial separation of rabbit liver S-RNA specific for proline, valine and leucine, and their properties are being compared. It has been found that molecular size is not important in determining the biological specificity of S-RNA for various amino acids. In addition there appears to be species specificity in the reaction between S-RNA and the activating enzymes.

Base composition of S-RNA suggests that this polynucleotide has a hydrogen-bonded structure. This conclusion has been reinforced by physicochemical and enzymological studies of S-RNA.

The requirements for transfer from S-RNA-AA to microsomes have been investigated systematically in the attempt to reduce the complexity of the system. (See also projects 16, 20, 22, 23, 26).

Scientific Significance:

Proposed Course of Research:

Part B included Yes X No ____

Part B.

Cantoni, G. L. Spermine fractionation of soluble RNA of rabbit liver. Nature, 1960, 188: 300.

Klee, Werner A., and Cantoni, G. L. Studies on soluble ribonucleic acid (SRNA) of rabbit liver. I. Amino acid acceptor specificity and molecular weight. Proc. Nat. Acad. Sci., 1960, 46: 322.

Serial No. M - CP 16
1. Lab. of Cellular Pharmacology
2.
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Amino Acid Activating Enzymes and Protein Synthesis

Principal Investigator: H. V. Gelboin, Ph. D.
G. L. Cantoni, M. D.

Other Investigators: None

Cooperating Units: None

Man Years:
Total: 1-1/3
Professional: 2/3
Other: 2/3

Project Description: (See Project M - CP 14)

Objectives:

Methods Employed:

The early steps involved in protein biosynthesis involve activation of amino acids and their incorporation into soluble ribonucleic acid. These reactions can be written as follows:

$$AA + ATP + ENZ \rightleftharpoons ENZ\text{-}AMP\text{-}AA + PP$$

$$ENZ\text{-}AMP\text{-}AA + SRNA \longrightarrow SRNA\text{-}AA + AMP + ENZ$$

The activation of amino acids have been measured by both of the above reactions, using $P^{32}P^{32}$ incorporation into ATP in the former and C^{14}-amino acid incorporation in SRNA in the latter reaction. Classical methods of enzymology, particularly the use of column chromatography, have been used in the purification of the enzymes.

Part A.

Major Findings:

Activating enzymes for all the common amino acids have been found in freshly prepared beef liver.

The proline activating enzyme, although very labile in the unpurified state has been purified 200-fold and can now be stored without appreciable loss of activity. The threonine activating enzyme has been purified 250-fold.

A number of the chemical properties of the proline activating enzyme have been determined. These include substrate affinity, substrate specificity, pH dependence, effects of various inhibitors, etc.

These purified enzymes have been used extensively in the study of the properties of soluble RNA.

Scientific Significance:

The availability of all the activating enzymes are a necessary adjunct to the study of protein biosynthesis (see CP - 14).

Proposed Course of Research:

Part B included Yes _____ No __X__

Serial No. M - CP 18
1. Lab. of Cellular Pharmacology
2.
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Studies on the Homogeneity and Polymerization of Thetin-homocysteine Methylpherase

Principal Investigator: Werner A. Klee, Ph. D.

Other Investigators: Giulio L. Cantoni, M. D.

Cooperating Units: None

Man Years:
Total: 1
Professional: 2/3
Other: 1/3

Project Description:

Objectives:

To establish the state of purity of the enzyme thetin-homocysteine methylpherase (THMPase) and to study the mechanism of the reversible polymerization of this enzyme as well as other properties of this protein. To study further the physiological role of the protein with the particular aim of elucidating the function, if any, of the polymerization reaction.

Methods Employed:

Major Findings:

It has been established that THMPase is an essentially pure protein preparation and that the enzymic activity and the polymerization are properties of the same protein species.

It has been found that the polymerization reaction results in a mixture of globular, rather than linear, polymeric molecules which range in sizes from monomer

Part A.

to large particles containing well over 50 monomer units. Electron microscopy has supported more indirect physicochemical measurements in demonstrating that all polymer molecules, no matter how large, are approximately spherical in shape.

The monomer unit itself, m.w. 200,000, can be cleaved by treatment with synthetic detergents into 3 or 4 smaller subunits of m.w. 50-60,000 and asymmetric in shape. There are indications that these subunits retain enzymatic activity. Thus, the enzyme protein appears to have unique and complex structural features.

In view of the discovery of a second enzyme (see CP 3, 1960) with more physiological substrate specificity the function of thetin-homocysteine methylpherase remains an open question.

Scientific Significance:

One of the principal objects of present day biochemistry is to try to understand the mechanism of enzyme action. A large class of enzymes is involved in transfer reactions of one kind or other and THMPase may be considered one of these. Apart from mechanistic considerations, however, it is apparent that the reversible polymerization which this protein can undergo is of interest in itself. One of the most obvious characteristics of living systems is the high degree of organization which is always found. Such organization implies that on the molecular level there are strong and specific interactions the nature of which is, in general, obscure. The highly specific interactions which THMPase molecules display towards each other in the polymerization reactions may be considered to be one kind of phenomenon which provides the organized structures of living cells. As such it deserves detailed study in order to firmly understand the nature and possible general significance of such phenomena.

Proposed Course of Research:

Part B included Yes X No ____

Part B.

Klee, W. A., and Cantoni, G. L. The synthesis of methionine by enzymatic transmethylation. VI. Studies of the homogeneity, shape properties and monomer functionality of thetin-homocysteine methylpherase. Biochim. Biophys. Acta, 1960, 45: 545-553.

Klee, W. A. The synthesis of methionine by enzymic transmethylation. V. Chromatographic analysis of thetin-homocysteine methylpherase on modified cellulose columns. Biochim. Biophys. Acta, 1960, 45: 537-544.

Serial No. M - CP 20
1. Lab. of Cellular Pharmacology
2.
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: A Study of Some of the Physicochemical Properties of "Soluble" Ribonucleic Acid (S-RNA)

Principal Investigators: S. W. Luborsky, Ph.D.
G. L. Cantoni, M. D.

Other Investigators: None

Cooperating Units: None

Man Years:
Total: 1-1/3
Professional: 2/3
Other: 2/3

Project Description:)
) See Project M - CP 14
Objectives:)

Major Findings

Work from this laboratory has resulted in the isolation from rabbit liver of a non-sedimentable RNA fraction (S-RNA) capable of accepting amino acid moieties and transferring them to the microsomal fraction in vitro. (See CP 14, 16, 21.)

The IBM 650 Computor was programmed for the rapid, precise calculation of the results of ultracentrifugation experiments performed on this material. These results indicate that amino acid active S-RNA exhibits a single symmetrical distribution of sedimentation coefficients, with a very low degree of heterogeneity, which is only slightly dependent upon the conditions of ionic strength or concentration. The asymmetrical distributions obtained from S-RNA preparations at earlier stages of purification were due to contamination with inactive material. The viscosity and density of solutions of this S-RNA preparation were determined, and the molecular

weight, calculated. The value obtained in this manner agreed well with that obtained in two independent ways in this Laboratory.

A two-phase system was devised in which the S-RNA could be distributed by countercurrent distribution. A three-fold purification of the valine-acceptor activity was obtained in this manner. Conditions were determined for the fractionation of the S-RNA by silica gel chromatography, using the above two-phase system. This work is being continued in the hope that S-RNA fractions specific to single amino acids can be obtained.

Scientific Significance:

This project is part of a larger laboratory program on protein biosynthesis.

Proposed Course of Research:

Part B included Yes ____ No X

Serial No. M - CP 23
1. Lab. of Cellular Pharmacology
2.
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Base Composition of SRNA

Principal Investigator: G. L. Cantoni, M. D.

Other Investigators: None

Cooperating Units: None

Man Years:
Total: 1-1/3
Professional: 2/3
Other: 2/3

Project Description:

Objectives:

To determine the base composition of SRNA.

Methods Employed:

SRNA, in contrast to other RNAs, contains bases other than cytidine, uracyl, adenine and guanine. There are about 8 of these minor bases and their exact distribution is unknown.

Major Findings:

A column chromatographic technique for the seperation and identification of the various purine and pyrimidine bases present in SRNA has been perfected. It is now possible to determine with great precision and reasonable speed the percent of distribution of cytidine, adenine, uridine, pseudouridine, guanine, thimidine and 2 methyl-6-hydroxypurine in SRNA, and with somewhat less precision the distribution of other small components. SRNA specific for different amino acids are being examined to determine whether there are significant differences in their base composition.

Part A.

Scientific Significance:

The project is part of a broader study of SRNA and its relationship to protein synthesis.

Proposed Course of Research:

Part B included Yes X No _____

Part B.

Singer, M., and Cantoni, G. L. Studies on soluble ribonucleic acid of rabbit liver. III. Terminal groups and nucleotide composition. Biochim. Biophys. Acta, 1960, 39: 182-183.

Serial No. M - CP 24
1. Lab. of Cellular Pharmacology
2.
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: The Biosynthesis of Hordenine

Principal Investigator: Jay D. Mann, Ph.D.

Other Investigators: None

Cooperating Units: None

Man Years:
Total: 1-5/6
Professional: 1
Other: 5/6

Project Description:

Objectives:

Within the general field of alkaloid biosynthesis, hordenine formation by germinating barley offers the advantages of simple structure, ready assay, and easily available plant material. A number of investigators have shown that hordenine (ß-p-hydroxyphenethyldimethylamine) appears suddenly during a specific stage of germination, and only at rapidly growing parts of the roots. It is hoped that study of the precursors and enzymes involved in hordenine biosynthesis may afford insights into more general questions of metabolic regulation.

Transmethylation reactions are frequently involved in the biosynthesis of many other alkaloids. Since two consecutive methylations are required in the conversion of tyramine to hordenine, these may serve as model reactions.

Methods Employed:

Major findings:

Crude homogenates of barley roots have been separated into two fractions, one containing a transmethylase specific for tyramine, the other a transmethlase acting on both tyramine and N-methyltyramine. S-adenosylmethionine is specifically required for both reactions, 2 x 10^{-6} M giving half-maximal rates. The affinity for tyramine and for N-methyltyramine is 1 x 10^{-5} M. pH 8.4 (Tris) gives maximal activity. For transmethylation of tyramine, the ΔH of activation is approximately 9200 calories. Generally, a DEAE-cellulose preparation is obtained, containing both enzymes about 300 fold purified over the crude homogenates.

Both enzymes are rapidly and irreversibly inactivated by p-chloromercuribenzoate or by the absence of sulfhydryl groups (ex., mercaptoethanol) in the medium. This may be a possible mechanism for metabolic control. Tyramine transmethylase is competitively inhibited by both N-methyltyramine and by hordenine (Ki = 3 x 10^{-4} M). In vivo, it is likely that these products are segregated in cell vacuoles and are not inhibitory. A third possible mode of metabolic control is the existence in crude extracts of an enzyme hydrolyzing S-adenosylmethionine to methylthioribose and an as yet unidentified compound.

Scientific Significance:

Both enzymes necessary for the final steps of hordenine biosynthesis can be purified and assayed. Correlation of enzymatic level with actual in vivo formation of hordenine in different root zones and at different ages may be of considerable interest.

Proposed Course of Research:

Work now planned concerns the distribution of enzymes and substrates along the root; the effect of metabolic inhibitors on enzyme synthesis; and the degree of substrate specificity for tyramine and N-methyltyramine transmethylases.

Part B included Yes _____ No X

Serial No. M - CP 25
1. Lab. of Cellular Pharmacology
2.
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: The Biosynthesis of Gramine

Principal Investigator: S. Harvey Mudd, M. D.

Other Investigators: None

Cooperating Units: None

Man Years:
Total: 1-1/3
Professional: 1/3
Other: 1

Project Description:

Objectives:

This project is part of the general program of investigation of alkaloid metabolic pathways. It complements the investigation of the biosynthesis of hordenine in that gramine is a dimethylamino compound also formed by germinating barley. By contrast, it contains the biologically important indole nucleus and is formed in the shoots.

Major Findings:

Two hitherto unknown compounds have been found in barley seedlings. These compounds are metabolic precursors of gramine. Their structure has been elucidated by synthesis, and by converting the compounds to appropriate derivatives. The enzymes which convert these sequentially to gramine have been estracted from barley and partially purified. (-)-S-adenosyl-L-methionine acts as a methyl donor for these enzymes as in other plant transmethylations.

Work is being carried on with there enzymes. Efforts are also being made to work out the earlier steps in biosynthesis of these compounds so that the overall pathway

from the amino-acid tryptophan to the alkaloids may be understood.

Scientific Significance:

Discussed in the reports on biosynthesis of hordenine of 1959 and 1960.

Proposed Course of Research:

Part B included Yes _____ No __X__

Serial No. M - CP 26
1. Lab. of Cellular Pharmacology
2.
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Studies on the Nucleotide Sequence in Rabbit Liver S-RNA

Principal Investigator: G. L. Cantoni

Other Investigators: Claude Blanc
Maxine Singer, Laboratory of Biochemistry and Metabolism, NIAMD

Cooperating Units: None

Man Years:
Total: 1-1/3
Professional: 2/3
Other: 2/3

Project Description:

Objectives:

There is reason to believe that the nucleotide sequence in RNA and DNA are of importance in determining the biological role of these compounds. The determination of nucleotide sequence in nucleic acid and its relation to the amino acid composition of protein is generally described in the "coding-problem."

S-RNA, because of its relatively small chain length, is a particularly suitable substrate for determination of nucleotide sequences, and for an approach to the so called "coding-problem."

Methods Employed:

Methods for the determination of nucleotide sequence are still in the developmental stage. The use of specific nucleases may give useful information; random cleavage of the polynucleotide chain followed by chromatographic separation of the fragments and their analysis by a

Part A.

combination of chemical, enzymological and spectrophotometric methods may also yield valuable data. These techniques are being explored pari passu with the attempts at isolation of S-RNA in pure form (see CP 14).

Major Findings:

S-RNA exhibits considerable resistance to a variety of nucleases. This may be due to the presence of secondary structure in S-RNA in contrast to most other RNA preparations.

By conventional procedures it has been established that all chains of S-RNA terminate with adenosine at the nucleoside end and with guanosine-5' phosphate at the distal (or nucleotide) end. The finding is of considerable significance both with respect to the homogeneity of the preparation of S-RNA and to the basis of its biological activity.

Preliminary results suggest that by a combination of enzymatic hydrolysis with pig liver and snake venom diesterases and chemical procedures an analogous series of fragments adjacent to the nucleoside terminal may be obtained. If these can be separated chromatographically or otherwise the road will be opened to determination of sequences of the chains starting from the nucleoside end.

Studies with the guanylic acid - specific ribonuclease of takadiastase are being developed also.

Scientific Significance:

The "coding" problem is one of the outstanding biological problems and any advance toward its solution would be a significant development. The RNA-protein coding problem is probably the simplest one of a number of coding mechanisms that are of importance in biology and information as to its mechanism may open for study other areas of relevance to biological investigation.

Part A.

Proposed Course of Research:

Part B included Yes X No _____

Part B.

Singer, Maxine F., and Cantoni, G. L. Studies on soluble ribonucleic acid of rabbit liver. III. Terminal groups and nucleotide composition. Biochim. Biophys. Acta, 1960, 39: 182-3.

Serial No. M - CP 27
1. Lab. of Cellular Pharmacology
2.
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: The Effects of Aromatic Amino Acids on Learning Ability and Cerebral Metabolism in the Rat

Principal Investigator: Seymour Kaufman, Ph. D.

Other Investigators: William Bridgers, M. D.
Theodore Goodfriend, M. D.*

Cooperating Units: Section on Aging, NIMH

Man Years:
Total: 1
Professional: 1/3
Other: 2/3

Project Description:

Objectives:

To determine the influence of dietary supplements of aromatic amino acids and their metabolites on learning behavior in the rat; to attempt an elucidation of the mechanism by which such an influence is exerted; and to investigate possible means for reversing or preventing such an influence.

Methods Employed:

Major Findings:

Preliminary experiments have shown that rats fed a stock diet learn to solve a "swimming maze" more quickly than litter-mates fed a diet containing 5% L-tyrosine, 3.75% sodium phenylpyruvate, or 3.75% D-phenylalanine. This finding has been observed in two separate experiments. Slight changes in rate of weight-gain and

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St. Louis 10, Mo.

Part A.

appearance of fur did not correlate with observed differences in learning ability. The diets were fed to lactating mothers and to weaned young. Tests were performed at 6 weeks of age.

Scientific Significance:

The availability of a reproducible change in learning ability in experimental animals as a result of a simple dietary alteration would offer an avenue of approach to the investigation of the biochemical basis of integrated nervous activity. Selection of the aromatic amino acids for investigation is made more appropriate by the existence of a human mutation, producing the disease phenylpyruvic oligophrenia, in which phenylalanine metabolism by the liver is impaired, and idiocy is observed. The relationship of the metabolic and mental defects is not known. The experiments proposed herewith are directed to finding whether or not an elevation in the blood level of one aromatic amino acid or metabolite thereof can result in impaired learning ability in the growing rat. Such a finding would therefore have the added significance of a tentative explanation of the pathogenesis of this disease, and might offer the basis for a practical therapeutic or prophylactic approach.

Proposed Course of Research:

The D- and L- isomers of phenylalanine, sodium phenylpyruvate, and other related compounds will be added to the diets of growing rats. Learning ability will be measured in the "swimming maze" and "light-avoidance" box. If one or more compounds are repeatedly implicated, their effects on the metabolism of brain tissue *in vitro* will be investigated.

Part B included Yes _____ No X

Serial No. M - CP 28
1. Lab. of Cellular Pharmacology
2.
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Genetic and Developmental Studies on Tryptophane Pyrollase in Drosophila Melanogaster

Principal Investigator: Seymour Kaufman, Ph. D.

Other Investigators: C. W. Clancy, Ph. D., Univ. of Oregon, Eugene, Oregon

Cooperating Units: None

Man Years:
Total: 1
Professional: 1/3
Other: 2/3

Project Description:

Objectives:

One of the major problems in biology today is the mechanism of gene action. For higher organisms, an intriguing aspect of this general problem is the role which genes play in cellular differentiation. Drosophila melanogaster would seem to be one of the most suitable organisms for studies of this kind since it provides a rich genetic and embryological background.

One of the most well studied mutants in D-melanogaster is the vermilion (v) mutant, where it is believed that the step between tryptophane and kynurenine is blocked. (In mammals, the enzyme which catalyzes this reaction has been isolated and named tryptophane pyrollase.) Since kynurenine is known to be a precursor of one class eye pigments, the v mutants are characterized phenotypically by having abnormal eye colors.

Part A.

About 20 years ago, it was observed that if v larvae are placed on a partial starvation diet, the eye color of the flies approaches normal pigmentation, i.e., partial starvation somehow leads to a functional repair of the genetic block. The main goal of this study is to determine how this block is repaired or bypassed in v mutants. It seems possible that any insight gained on this problem may have implications for our understanding of the relationship between genes and specific cellular proteins.

Methods Employed:

An assay procedure for the enzyme has been devised which is sensitive enough to detect activity in 20-30 wild-type flies. To provide material for this study, standard methods of drosophila breeding and culture are being used.

Major Findings:

There are no major findings as yet since the time has been devoted to the devising of a sensitive assay. It has been found that in wild-type flies, the enzyme is not present in the larval stage but begins to appear shortly after puparium formation. As might have been expected, no enzyme activity has been found in v mutants.

Scientific Significance:

It is too early to discuss the significance.

Proposed Course of Research:

Extracts of starved v flies will be assayed for the tryptophane-pyrollase. If the enzyme can be detected, the mechanism for its appearance will be studied. If the enzyme cannot be detected, metabolic pathways which could bypass the block will be explored.

Part B included Yes _____ No X

Serial No. M-AR-1 (c) -1
1. Addiction Research Center
2. Clinical Investigations
3. PHS Hospital, Lexington, Ky.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Addictive Liabilities of New Analgesics

Principal Investigator: H. F. Fraser

Other Investigators: A. B. Wolbach, Jr., and W. R. Martin

Cooperating Units: Laboratory of Chemistry, Section on Analgesics, NIAMD. The Office of Naval Research provided $38,800 in fiscal year 1960 and $45,000 in fiscal year 1961 to carry on investigations designed to develop synthetic substitutes for codeine. This fund provided salaries for 7 subprofessional employees working seven man years. The NIMH Addiction Research Center provided administrative and supervisory services amounting to 1-1/3 man years.

Man Years (cal. yr. 1960):		Patient Days (cal. yr. 1960):
Total:	8-1/3	4871
Professional:	1-1/3	
Other:	7	(Not chargeable to Clinical Center)

Project Description:

Objectives. 1) To develop drugs effective in relieving pain, cough and diarrhea, with lesser addictive potential than morphine, and 2) to supply information on the addictive properties of new drugs prior to release for general sale. The latter objective is carried out in collaboration with the Committee on Drug Addiction and Narcotics of the National Research Council, and is designed to prevent uncontrolled use of potentially addicting drugs.

Methods Employed. Drugs are referred to the NIMH Addiction Research Center by the Committee on Drug Addiction and Narcotics of the National Research Council. The Addiction Research Center, using former addict volunteers with prisoner status, determines: 1) the psychological and physiological effects of single doses of new drugs, 2) whether the new drugs will relieve or suppress abstinence from morphine, and 3) in some cases, whether patients who are not tolerant to morphine can be directly addicted to the new drug.

Patient Material	No.	Average Stay (days)
Admissions:	60	81
Outpatients:	59	
No. of visits:	350	

(Note: This patient material is not chargeable to the Clinical Center)

Major Findings.

1. Opiate "attitude" questionnaires which provide for independent addictive "ratings" of drugs by former opiate addicts and by observers have been extended to include additional drugs and three routes of administration (oral, subcutaneous and intravenous). The addictive "ratings" of opiate addicts for a series of morphine-like drugs respecting identification as "dope" (opiate), "strength" (potency), and extent to which they "would like to take each drug daily" covaried with the intensity of the abstinence syndrome which developed when each of these drugs was discontinued abruptly. Degree of "acceptance" of drugs by addicts was significantly influenced by the route of administration; for example, positive "acceptance" of morphine was zero by

the oral route, 40 per cent when given subcutaneously, and 54 per cent by the intravenous route. Heroin had an "acceptance" rating of 32 per cent subcutaneously, as compared to 76 per cent intravenously. All of these studies were conducted on a double-blind basis, i.e., neither subjects nor observers knew the nature or schedule of the medication given.

2. Addiction liability studies were completed on seven new compounds. Reports on two of these, phenampromid and diampromid, have been submitted to the Committee on Drug Addiction and Narcotics, National Research Council, and the latter recommended that they be placed under narcotic control. One compound, an isoquinoline derivative (ARC I-K-1), is reported to possess analgesic potency comparable to codeine but it is less addictive than either codeine or d-propoxyphene as judged by studies in postaddicts.

Scientific Significance. Reports rendered to the National Research Council are the basis for recommendations concerning appropriate legal action connected with the control of these drugs at national and international levels. This prevents introduction of potentially addictive substance into uncontrolled use, thereby minimizing addiction to new drugs. Because of the large number of drugs being synthesized future studies should reveal better dissociations of desirable pharmacological properties (analgesic, antitussive, and antidiarrheal) from addictive characteristics. The psychological effects and mechanisms of action of these new drugs are frequently of great theoretical interest in the field of mental health.

Proposed Course of Project. The program will be continued and drugs referred by the Committee on Drug Addiction and Narcotics will be tested as rapidly and completely as facilities permit. Emphasis will be placed on the development of improved quantification of the methods used, on dissociations in drug effects, and on the relative addictiveness of drugs when administered intravenously.

Part B included: Yes

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Individual Project Report
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Part B. Honors, Awards, and Publications

Publications other than abstracts from this project:

1. Fraser, H. F. and Isbell, H.: Human pharmacology and addictiveness of ethyl 1-(3-Cyano-3,3-phenylpropyl)-4-piperidine carboxylate hydrochloride (R-1132, Diphenoxylate). Bull. Drug Addiction and Narcotics. add 2, pp 1-34. Min. 21st Meet., Committee on Drug Addiction and Narcotics, NRC. Washington, D.C. Natl. Acad. Sci. (Jan.) 1960.

2. Fraser, H. F., Van Horn, G. D., Martin, W. R., and Isbell, H.: New methods for evaluating addiction liability of morphine-like drugs. I. Attitude of opiate addicts toward drugs. II. Short-term direct addiction procedure. Bull. Drug Addiction and Narcotics. p 2272, app. 11, p 1-27, Min. 21st Meet., Committee on Drug Addiction and Narcotics, NRC. Washington, D.C. Natl. Acad. Sci. (Jan.) 1960.

3. Fraser, H. F., Isbell, H., and Wolbach, A. B.: Addictiveness of new synthetic analgesics. I. Benzimidazole derivatives: (a) 2-(p-Chlorobenzyl)-1-diethylaminoethyl-5-nitrobenzimidazole methane sulfonate (NIH-7586, ARC I-G-1), and (b) 2-(p-Ethoxybenzyl)-1-diethylaminoethyl-5-nitrobenzimidazole hydrochloride (NIH-7607, ARC I-G-2); II. (-) 3-Hydroxy-N(3,3-dimethylallyl)-morphinan hydrobromide (NIH-7446); III. (a) N-(1-Methyl-2-piperidinoethyl-propioanilide hydrochloride (Phenampromid), and (b) N-[2-(Methyl)-phenethylamino)-propyl]-propioanilide sulfate (Diampromid). Bull. Drug Addiction and Narcotics, add. 2, pp 35-51, Min. 21st Meet., Committee on Drug Addiction and Narcotics, NRC. Washington, D.C. Natl. Acad. Sci. (Jan.) 1960.

4. Fraser, H. F. and Isbell, H.: Pharmacology and addiction liability of dl- and d-propoxyphene. Bull. Narcotics 12: (1) 9-14 (Jan.-Mar.) 1960.

5. Fraser, H. F. and Isbell, H.: Human pharmacology and addiction liabilities of phenazocine (NIH-7519) and levophenacylmorphan (NIH-7525). Bull. Narcotics 12: (2) 15-23 (Apr.-June) 1960.

6. Fraser, H. F. and Isbell, H.: Human pharmacology and addiction liability of norcodeine. J. Pharmacol. & Exper. Therap. 129: 172-177 (Feb.) 1960.

Honors and Awards relating to this project:

Isbell, H.:

1. By invitation, presented lecture at laboratories of Hoffman-La Roche, Basle, Switzerland, on "Addiction liability testing," 2 November 1959.

2. By invitation, presented lecture, "Current pharmacological and psychiatric approaches to addiction," to Danish Psychiatric and Pharmacological Societies, Copenhagen, Denmark, 25 November 1959.

3. By invitation, presented University Lecture on "Pharmacology of opiate addiction," Kings College, University of London, England, 26 February 1960.

4. By invitation, presented the Eighth Kelynack Memorial Lecture, "Perspectives in research on opiate addiction," British Society for the Study of Addiction, London, England, 29 March 1960.

5. By invitation, participated in Symposium on Drug Addiction, presenting a paper on "Pharmacology of the opiates and similar addiction-producing drugs," at a meeting of the Section on Neurology, Royal Society of Medicine, London, England, 7 April 1960.

Fraser, H. F.:

Served as Chairman, Section on Analgesics, Meeting of American Society for Pharmacology and Experimental Therapeutics, Seattle, Washington, 21-25 August 1960.

Serial No. M-AR-2 (c) - 1
1. Addiction Research Center
2. Clinical Investigations
3. PHS Hospital, Lexington, Ky.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Acute and Chronic Intoxication with Drugs Other Than Analgesics, Barbiturates, or Alcohol.

Principal Investigator: Harris Isbell

Other Investigators: Abraham Wikler and A. B. Wolbach, Jr.

Cooperating Units: Psychiatric Service, Clinical Division, PHS Hospital, Richard Chessick

Man Years (cal. yr. 1960):		Patient Days (cal. yr. 1960):
Total:	5	1294
Professional:	1	
Other:	4	(Not chargeable to Clinical Center)

Project Description:

Objectives. To determine the subjective and objective effects and pathologic physiology of drugs other than those in the barbiturate, opiate, and alcoholic classes. The drugs studied are of importance in that they 1) may be abused by opiate addicts, 2) are reported to be of value in the treatment of addiction, 3) are reported to be of value in treatment of mental disease, and 4) produce profound psychological effects.

Methods Employed. Appropriate doses of the drugs are administered acutely or chronically to former morphine addict volunteers in the ARC, and selected schizophrenic nonaddicts in the Psychiatric Service. Physiological, psychological, and clinical measurements are made before, during, and after intoxication.

Patient Material		No.	Average Stay (days)
Admissions:	Adult males	20	65
	Outpatients	20	
	No. of visits	124	(Not chargeable to Clinical Center)

Major Findings. Definite cross tolerance to both objective and subjective effects developed between LSD-25 and psilocybin following chronic administration of either drug for 6-12 days. Increasing the dosage and length of administration of psilocybin did not enhance the degree of direct tolerance to psilocybin and cross tolerance to LSD.

Schizophrenic patients develop tolerance to the "objective" effects (pupillary dilatation) of LSD as rapidly and as completely as do nonschizophrenic former addicts. The degree of response of the pupils to a given dose of LSD may be less in nontolerant schizophrenics than in nontolerant nonschizophrenic addicts.

Mescaline causes the same types of autonomic and mental changes as does LSD. Mescaline is only 1/3000th as potent as LSD. Psilocin, the dephosphorylated derivative of psilocybin, is 1/50th as potent as LSD when given intramuscularly. Studies on direct and cross tolerance between mescaline and LSD are in progress.

Scientific Significance. The psychotomimetic drugs continue to provide means of safely inducing psychotic states in human volunteers. Various metabolic and toxic theories of the etiology of natural psychoses have been based on the effects of these drugs. Interactions of the psychotomimetic agents with tranquilizers, hormones, sympathomimetic blocking agents, etc., represent one way of testing these hypotheses. Specific groups of psychotomimetics may be differentiated by tolerance and cross tolerance techniques and these groups may give important clues to the mode of action of psychotomimetic drugs.

Proposed Course of Project. Studies on tolerance and cross tolerance to mescaline and LSD-25 (now underway) will be completed. Related experiments will then be undertaken with amphetamines, and cholinergic blocking agents, e.g., scopolamine and the dibenzylates, in the hope of separating the psychotomimetic drugs into separate groups by means of the tolerance-cross tolerance technique.

Part B included: Yes

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B. Honors, Awards, and Publications

Publications other than abstracts from this project: None

Honors and Awards relating to this project:

Isbell, H.:

1. Lectures, by invitation, "Studies on hallucinogenic drugs," Sandoz Laboratories, and the University of Basle, Basle, Switzerland, 2 November 1959.

2. By invitation, presented paper "Cross tolerance between LSD and psilocybin," Regional Meeting (Kentucky), American College of Physicians, Lexington, 29 October 1960.

3. Became Editor-in-Chief for United States and Canada, Psychopharmacologia, July 1960.

Serial No. M-AR-3 (c) - 1
1. Addiction Research Center
2. Clinical Investigations
3. PHS Hospital, Lexington, Ky.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Clinical Studies of Intoxication with Alcohol, Barbiturates, and Related Drugs.

Principal Investigator: C. A. Haertzen

Other Investigators: H. E. Hill

Cooperating Units: Hospital Division, U. S. Public Health Service (one study); University of Minnesota, Minneapolis, and Willmar State Hospital, Willmar, Minn. (one study).

Man Years (cal. yr. 1960):		Patient Days (cal. yr. 1960):
Total:	2-1/3	None
Professional:	2/3	
Other:	1-2/3	

Project Description:

Objectives. 1) To investigate the psychopathology of alcoholism, 2) to determine the clinical characteristics of acute intoxication with alcohol, barbiturates, and related drugs, and 3) to study possible relationships between personality characteristics and specific effects of such drugs.

Methods Employed. By use of appropriate instruments (Minnesota Multiphasic Personality Inventory, Inventory of Habits and Attitudes, Guilford-Zimmerman Temperament Survey), the personality characteristics and attitudes of narcotic addicts are compared with those of normal groups, and other institutionalized groups (alcoholics, criminals without alcoholism or narcotic addiction). Subjective effects of acute doses of alcohol and barbiturates are studied in randomized order with other drugs, by administering the ARC Inventory and the Guilford-Zimmerman test to subjects before and after various doses of these drugs. Statistical procedures are then used to isolate common and specific actions and relate these drug effects to differential personality characteristics.

Patient Material	No.	Average Stay (days)
Admissions:	None	--
Outpatients:	96	
No. of visits:	464	

Major Findings. Application of two forms of inverted factor analysis to previously obtained MMPI profiles of institutionalized groups (200 narcotic addicts, 200 alcoholics and 200 criminals) produced a first and common factor of social deviance. This characteristic was so heavily loaded in all three groups that no factor independent of such psychopathic traits was found. This dominating influence was combined with indications of neurotic and schizoid tendencies in other factors, none of which however were sufficiently differentiating to be diagnostic. Work on the Inventory of Habits and Attitudes was held in abeyance (until 1961). Analysis of the ARCI data on alcohol and pentobarbital has progressed through development of "primary" and "secondary" effects, as shown in Serial No. M-AR-6 (c) for various other drugs. Methods for distinguishing specific and non-specific effects within this instrument are being explored. In contradistinction to one prominent theory, marked subjective effects of alcohol are more likely to be reported by the emotionally unstable, depressed individual, as indicated by use of the Guilford-Zimmerman test with addict samples.

Scientific Significance. Alcoholism is a major health problem. Research in this area is therefore urgently needed. The finding of commonalty of social deviance in alcoholics, narcotic addicts and criminals within the limits of the MMPI, suggests strongly that psychopathic personality is specific to neither alcoholics nor narcotic addiction, nor to the addictions in general, although it may be a general predictor of such deviant behavior. Measurement of subjective effects (for example, by the ARCI) is a necessity if progress is to be made in understanding and predicting the use and misuse of alcohol, barbiturates and related drugs.

Proposed Course of the Project. Studies on common and differential characteristics of alcoholics and addicts and other social deviants will be continued. Various analytic technique will be applied to the ARCI data in attempts to isolate specific and non-specific actions of alcohol and barbiturates, and to relate such actions to distinguishing characteristics of behavior.

Part B included: Yes

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B. Honors, Awards, and Publications

Publications other than abstracts from this project:

Hill, H. E., Haertzen, C. A., and Glaser, R.: Personality characteristics of narcotic addicts as indicated by the MMPI. J. Gen. Psychol. 62: 127-139, 1960.

Honors and Awards relating to this project:

Wikler, A.:

By invitation, presented paper "Survey of research on alcohol at the NIMH Addiction Research Center," at the 26th International Congress on Alcohol and Alcoholism in Stockholm, Sweden, 31 July-5 August 1960.

Isbell, H.:

By invitation, presented lecture, "Work of the NIMH Addiction Research Center," J. R. Geigy Laboratories, Basle, Switzerland, 6 November 1959.

Serial No. M-AR-4 (c) - 1
1. Addiction Research Center
2. Clinical Investigations
3. PHS Hospital, Lexington, Ky.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Biochemistry of Addiction

Principal Investigator: Anna J. Eisenman

Other Investigators: Jewell W. Sloan

Cooperating Units: Dept. Pharmacology-Toxicology, University of Wis., G. J. Mannering, Ph. D., Associate Prof.

Man Years (cal. yr. 1960):		Patient Days (cal. yr. 1960):
Total:	2-2/3	416
Professional:	2/3	
Other:	2	(Not chargeable to Clinical Center)

Project Description:

Objectives. To determine changes in chemistry of body fluids and organs arising from acute and chronic administration of drugs; determine rate, nature of conjugation and destruction as well as the distribution of drugs in the body; ascertain route and rate and duration of excretion of drugs.

Methods Employed. Standard methods of clinical biochemistry and chemical pharmacology are adapted to the special requirements of the individual experiments. Measurements of concentrations of drugs, their metabolites and of various natural compounds are made before, during and after acute or chronic administration of drugs.

Patient Material	No.	Average Stay (days)
Admissions:	8	52
Outpatients:	36	
No. of visits:	36	

Major Findings.

Normorphine. The work on normorphine was interrupted before we could find a method of obtaining pure bound normorphine.

Metabolism and excretion of heroin and codeine (collaborative experiment with Dr. Mannering). Patients were addicted to high (76 mg/day) and (low 8 mg/day) doses of heroin and codeine. The codeine dosages were 1,500 and 80 mg/day. Nicotine proved to be an unexpected interferent in the Mannering method for the extraction, identification and quantitation of morphine excreted after heroin administration. Finally a method was devised (chromatographic separation and quantitative estimation by the silicomolybdic acid method). Results are reserved pending confirmation by Dr. Mannering. The codeine samples have been extracted but final quantitation remains to be done.

Detection of drugs for the clinical service. Tranquilizers interfere with the spot test detection of opiate drugs and barbiturates in the urine. The method for opiates in use was replaced by Mannering's method of extraction and chromatography. Positive chromatographs were determined by R_fs as compared with those of standard morphine and codeine. Positives were eluted and tested with Marquis and Froehde spot reagents. New urinary barbiturate tests tried have proved satisfactory only where a high concentration is present. Several experiments on blood barbiturates proved moderately successful. Demerol has been identified by successive chromatography. The solvent system used for morphine will give a positive R_f. Where demerol is present, it has been eluted and rechromatographed in an appropriate solvent system: tertiary amyl alcohol, butyl ether, water. In this system, nordemerol and demerol gave seperate R_fs.

Catechol amines. The Crawford and Low method, reported as being in process of trial last report, proved unsatisfactory.

Scientific Significance. Understanding of effects of drugs on chemical processes in the body is basic to understanding of the subjective effects produced by these drugs, and hence to understanding of addiction. Differences in distribution, metabolism and excretion may account for many of the differences in addictiveness of the various drugs.

Proposed Course of Project. When the collaborative project with Dr. Mannering is terminated, work on the isolation of normorphine will be resumed. We have acquired a Liquid Scintillation Counter and shall have radio-tracer techniques. Work on animals will be initiated. Chemical analyses and radio-techniques will be employed in studies of the concentrations and distribution of adrenaline and nor-adrenaline. Animal experiments will be used. In collaboration with the Social Service Department of the hospital we shall be engaged in a study on discharged subjects, which will involve analyses of urines for opiates, barbiturates and demerol.

Part B included: Yes

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B. Honors, Awards, and Publications

Publications other than abstracts relating to this project: None

Honors and Awards relating to this project:

Eisenman, A. J.:

Appointed member, Committee of Experts for United Nations' Program of Opium Research, Division of Narcotic Drugs, United Nations.

Serial No. M-AR-5 - 1
1. Addiction Research Center
2. Experimental Neuropsychiatry
3. PHS Hospital, Lexington, Ky.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Neurophysiology and Neuropharmacology of Chronic Intoxication with Barbiturates, Alcohol and Related Drugs.

Principal Investigator: C. F. Essig

Other Investigators: H. G. Flanary

Cooperating Units: None

Man Years (cal. yr. 1960):		Patient Days (cal. yr. 1960):
Total:	3	None
Professional:	1	
Other:	2	

Project Description:

Objectives. To determine the effects on the central nervous system of chronically administering and abruptly withdrawing sedative and tranquilizing drugs. This year the role of the cerebral cortex in convulsions following abrupt barbiturate withdrawal has been emphasized.

Methods Employed. Bilateral ablation of the cerebral cortex was accomplished in 12 dogs prior to administering increasing amounts of sodium barbital for 202 to 283 days. Three dogs survived, and abrupt withdrawal was carried out at final dosages of 128 to 168 mg/kg. Three intact dogs were intoxicated and withdrawn on comparable schedules.

Major Findings. During the week of withdrawal, continuous observation revealed that each of the 3 control dogs had one or more major convulsion, but none of the decorticate dogs had fits. One decorticate dog had two 20-minute episodes of violent motor behavior, salivation, and barking, all of which resembled sham rage.

Scientific Significance. Since the decorticate dog can have metrazole induced convulsions, it appears that an intact cerebral cortex may be necessary for the occurrence of barbiturate withdrawal convulsions. However, the convulsive process may not originate in the cerebral cortex. Thus, one dog evinced episodes of furor suggesting that convulsions may have occurred if the cerebral cortex had been intact.

Proposed Course of Project. Two of the decorticate dogs are being reintoxicated in order to reach exceedingly high final dose levels of barbiturate. Abrupt withdrawal could result in truncated seizures of brain stem origin. This result would indicate that barbiturate withdrawal convulsions do not originate in cerebral cortex but that it lowers the threshold for their occurrence as well as participating in or influencing the motor pattern of the seizure.

Part B included: Yes

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B. Honors, Awards, and Publications

Publications other than abstracts from this project:

1. Essig, C. F. and Flanary, H. G.: Convulsions in cats following withdrawal of barbital sodium. Exper. Neurol. 1: 529-533, 1959.

2. Essig, C. F.: The Barbiturate Withdrawal Syndrome. A Clinical and Electroencephalographic Study. By Munke Hertel Wulff. (Thesis, M. D., University of Copenhagen). Electroencephalog. and Clin. Neurophysiol. supp. 14, pp. 173. Ejnar Nunksgaard, Nørregade 6, Copenhagen, K. Denmark, 1959. J. A. M. A. 171: (1) 260-261, 1959.

Honors and Awards relating to this project:

Essig, C. F.:

Appointed lecturer in pharmacology, University of Louisville School of Medicine, Louisville, Kentucky.

Elected member, Kentucky Academy of Science.

Serial No. M-AR-6 (c) - 1
1. Addiction Research Center
2. Experimental Neuropsychiatry
3. PHS Hospital, Lexington, Ky.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Psychological Studies of Addiction

Principal Investigator: Harris E. Hill

Other Investigators: R. S. Yamahiro, C. A. Haertzen, and H. G. Flanary

Cooperating Units: None

Man Years (cal. yr. 1960):		Patient Days (cal. yr. 1960):
Total:	5-2/3	None
Professional:	4-1/3	
Other:	1-1/3	

Project Description:

Objectives. To develop refined methods for measuring specific and common subjective effects of analgesic, hypnotic, tranquilizing, analeptic and psychotomimetic drugs. To relate differential measures of such effects to personality characteristics. To develop clinical and experimental techniques for analyzing variables which control behavior in the psychopath, and to determine the patterning of controls which are differentially related to the misuse of opioids and alcohol. To develop animal methods for screening analgesic and other classes of drugs. To investigate drug-produced changes in learning and retention, with emphasis on anxiety.

Methods Employed. The ARC Inventory for differentiating subjective drug effects is given to healthy subjects without medication, and after administration of a placebo and various doses of morphine, chlorpromazine, amphetamine, LSD-25, and marihuana-like compounds. Refined statistical techniques are then applied to the data. Personality tests are given to the same subjects without drugs. Methods involving learning and retention under drug and no-drug conditions are utilized in relation to the performance of psychopaths and normals. In rats, morphine, pentobarbital, reserpine, amphetamine, nalorphine, cocaine, and LSD-25 are studied with respect to their effects on conditioned emotional responses and on auditory discrimination. Also in rats, learning and retention in a traumatic avoidance situation are studied before and after administration of Ecolid, a ganglionic blocking agent.

Patient Material	No.	Average Stay (days)
Admissions	None	--
Outpatients	96	
No. of visits	902	

Major Findings. Cross-validation of the ARC Inventory on two groups of 50 subjects, and checking results on a third group, produced scales of items which discriminated all above mentioned drugs from a placebo. These scales are comprised of items which indicate primary and secondary effects separately for each drug mentioned above. Analytic methods for defining specific and non-specific drug actions and

their relation to personality have been explored. On the basis of partial evidence, "choice" behavior of normal subjects in an experimental situation is more nearly approximated by postaddicts under morphine than under no-drug conditions. In rats, chronic reserpine, in common with other non-analgesics, produced little or not attenuation of conditioned anxiety. Tentative results suggest that amphetamine impairs auditory discrimination but that morphine and pentobarbital do not. Ecolid produces autonomic blockade in the unmedicated rat and reduces the strength of a previously conditioned traumatic avoidance response.

Scientific Significance. Quantification and differentiation of subjective drug effects is essential to further progress in psychopharmacological research. Analysis of variables which control behavior in the psychopath may lead to improved understanding of this socio-psychological deviant and may yield information on factors which differentially contribute to narcotic addiction, alcoholism and criminality. Development of a reliable method for screening analgesics and other drugs may be of considerable value in discovering new analgesics and in elucidating psychological mechanisms involved in pain and its relief. Investigation of effects of drugs on learning, "forgetting," and extinction, may provide methods of predicting and therapeutically controlling emotion and mental illness.

Proposed Course of Project. Factor analysis and other statistical techniques will be used on the ARCI data in attempts to further define specificity and commonalty of drug actions. Current and new experimental methods will be used to investigate motivations and their alteration by drugs in the psychopath. In rats, the analgesic screening methods and ancillary studies will be continued, as will investigations of drug-produced alteration of conditioned anxiety.

Part B included: Yes

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B. Honors, Awards, and Publications

Publications other than abstracts from this project: None

Honors and Awards relating to this project:

Isbell, H.:

1. By invitation, lectured on "Research program of the NIMH Addiction Research Center," to Medical Staff, Maudsley Hospital, London, England, 26 February 1960.

2. By invitation, lectured on "Research on drug addiction in the United States," to faculty and students, Medical School of University of Berne, Switzerland, 2 December 1959.

Wikler, A.:

By invitation, presented seminar on "Philosophy of research on psychopharmacology," to Department of Pharmacology, University of Michigan Medical School, Ann Arbor, Michigan, 9 May 1960.

Hill, H. E.:

Elected member, Kentucky Academy of Science.

Serial No. M-AR-7 -1
1. Addiction Research Center
2. Experimental Neuropsychiatry
3. PHS Hospital, Lexington, Ky.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: The Mode of Action of Central Nervous System Depressants

Principal Investigator: W. R. Martin

Other Investigators: Anna J. Eisenman

Cooperating Units: None

Man Years (cal. yr. 1960):		Patient Days (cal. yr. 1960):
Total:	4-1/3	None
Professional:	2/3	
Other:	3-2/3	

Project Description:

Objectives. To determine neurophysiological mechanism responsible for the opiate withdrawal syndrome.

Methods Employed. Three preparations have been employed in this project: 1) The effects of single subcutaneous doses of morphine (10 mg/kg) and nalorphine (20 mg/kg) as well as the effect of intravenously infused morphine (3 mg/kg/hr for 8 hrs) and post infusion nalorphine (20 mg/kg) have been studied in the intact dog. Pulse rate, respiratory rate, body temperature, pupillary diameter, skin twitch, and withdrawal reflex and behavioral states were observed and recorded. In addition signs of abstinence (rhinorrhea, lacrimation, salivation, tremor, etc.) were tabulated; 2) the effect of the above mentioned dosage schedules of morphine and nalorphine were studied in the spinal dog (T10-T11). In addition to the above mentioned observations, the patellar, extensor thrust, crossed extensor and ipsilateral flexor reflexes were studied; 3) the effects of nalorphine (10 mg/kg) and morphine (20 mg/kg) plus nalorphine (10 mg/kg) on respiratory rate, pulse rate, EEG, plasma CO_2 concentrations, plasma pH and hematocrit of the cerveau isolé cat were also studied.

Major Findings. During infusion of morphine, the pupillary diameter, skin twitch, and withdrawal reflex became maximally depressed within two hours after the beginning of infusion, and thereafter showed evidence of decreasing depression. In addition, a test dose (10 mg/kg s. c.) of morphine administered 17 hours following infusion was significantly less effective than a pre-infusion dose of the same magnitude in depressing the skin twitch and the withdrawal reflex. These findings indicate that definite signs of tolerance can be obtained during and following a short (8 hour) infusion of morphine.

Administration of nalorphine (20 mg/kg) following an 7-1/2 to 8 hour infusion of morphine (3 mg/kg/hr) produced a dramatic syndrome which consisted of marked restlessness, violent tremors, lacrimation, salivation, rhinorrhea, defecation, urination, acceleration of respiratory rate, marked tachycardia, mydriasis, and a rapid increase in body temperature.

A post infusion injection of nalorphine (20 mg/kg) in spinal dogs produced similar signs, but in addition caused extensor hypertonus of the hindlegs, inhibited the extensor thrust, increased the sensitivity for evocation of running movements in the hindlimbs and increased the magnitude of the crossed extensor and ipsilateral reflex above that observed following either nalorphine or morphine.

These signs in the intact and spinal dog resembled abstinence signs observed in dogs chronically addicted to morphine, and indicate that physical dependence can be consistently produced following a single infusion of morphine.

Administration of morphine (20 mg/kg) to the feline cerveau isolé preparation depressed respiratory rate (e.g., RR 19 to 10), caused hypercapnia and increased serum pH slightly. Administration of nalorphine (10 mg/kg) following morphine (20 mg/kg) produced a marked tachypnea (e.g., RR = 10 to 35) which gradually diminished to a modest increase in respiratory rate (2 or 3 breath per minute over the control level), hypocapnia and a slight but significant serum alkalosis.

Scientific Significance. Schmidt and Livingston have previously shown that acute tolerance can be produced by single massive doses of morphine, and Wikler and his collaborators have found that nalorphine following single massive doses of morphine produced physical dependence. These studies have confirmed those of the above mentioned workers, but in addition have provided a method for quickly and reproducibly inducing tolerance and physical dependence to morphine, which may be useful as a screening method for rapidly assessing the addiction liability of new drugs. In addition, in allowing the rapid production of tolerance and physical dependence, a method has been established which permits application of neurophysiological techniques in acute experiments.

In elucidating the physiological factors responsible for signs of physical dependence, rapidly changing homeostatic levels seem to be of great importance. As an example, morphine establishes a homeostatic level that differs from the control homeostatic level in that blood CO_2 levels are much higher. Nalorphine establishes a homeostatic level in which blood CO_2 levels are lower than control values. When nalorphine is administered after morphine, the homeostatic level is rapidly shifted from a state in which high blood levels of CO_2 is the equilibrium condition to one in which lower blood levels of CO_2 are the equilibrium state. Since these homeostatic levels can be altered at a very rapid rate pharmacologically, violent increases in respiratory intercharge are initiated to establish new equilibrium conditions.

Proposed Course of Project. Investigations concerning how morphine and nalorphine alter the homeostatic level of the hypothalamic thermoregulatory mechanism and the effect of rapidly altering this level on heart rate, respiratory rate and myographic activity are now in progress. In addition to studying physiological mechanisms involved in the production of signs of acute physical dependence, investigations are underway to determine if "pharmacological redundancy" can be demonstrated for systems other than the EEG activating and midbrain vasomotor systems, as well as for drugs other than atropine. Pharmacological redundancy may be an important principle in the development of tolerance.

Part B included: Yes

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B. Honors, Awards, and Publications

Publications other than abstracts from this project:

1. Longo, V. G., Martin, W. R. and Unna, K. R.: A pharmacological study of the "Renshaw" cell. J. Pharmacol. & Exper. Therap. 129: (1) 61-68, 1960.

2. Martin, W. R., Riehl, J. L., and Unna, K. R.: Chlorpromazine III. The effects of chlorpromazine and chlorpromazine sulfoxide on vascular responses to l-epinephrine and l-arterenol. J. Pharmacol. & Exper. Therap. 130: (1) 37-45 (Sept.) 1960.

3. Martin, W. R., and Eades, C. G.: A comparative study of the effects of drugs on activating and vasomotor responses evoked by midbrain stimulation: atropine, pentobarbital, chlorpromazine and chlorpromazine sulfoxide. Psychopharmacologia, 1: 303-335, 1960.

Honors and Awards relating to this project:

Martin, W. R.:

1. Appointed lecturer in pharmacology, University of Louisville School of Medicine.

2. Elected member, Kentucky Academy of Sciences.

3. By invitation, gave seminars at Dept. of Pharmacology, Baylor University, Houston, Texas, on "The effects of drugs on the spinal cord," and "The effects of drugs on the brain stem," 5 October 1960.

4. By invitation, gave seminar on "New methods of evaluating addiction liability," at Dept. of Pharmacology, University of Illinois Medical School, Chicago, Ill., 10 November 1960.

Serial No. M-AR-8 -1
1. Addiction Research Center
2. Experimental Neuropsychiatry
3. PHS Hospital, Lexington, Ky.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: "Conditioning" Factors in Addiction and Habituation (Relapse).

Principal Investigator: Abraham Wikler

Other Investigators: P. C. Green and F. T. Pescor

Cooperating Units: None

Man Years (cal. yr. 1960):		Patient Days (cal. yr. 1960):
Total:	3-2/3	None
Professional:	1	
Other:	2-2/3	

Project Description:

Objectives. To test the hypotheses that 1) recurrence of drug-seeking behavior following withdrawal from an addicting drug is due partly to "conditioning" processes generated during addiction, through repeated temporal association of specific stimuli (environmental events or activities of the organism) with the occurrence of abstinence phenomena, and/or their reduction by administration of the drug, and 2) the permanence of such "conditioning" is positively related to the effort expended by the organism in activities which culminate periodically in administration of the drug.

Methods Employed. Work on this multi-faceted and continuing project during 1960 was confined to 1) basic pharmacological studies, and 2) initial conditioning studies of morphine and a more potent, faster acting opioid (the benzimidazole derivative, I-G-2). The purposes of these investigations were to develop valid and reliable methods of measuring tolerance to and abstinence from the above drugs, and to test preference for I-G-2 or water in rats addicted by daily morphine injections from which opioids had been withheld for various periods of time. The studies consisted of: a) permitting rats to obtain all fluid intake from tubes containing progressively increasing concentrations of I-G-2 and testing for physical dependence by measuring signs of abstinence following nalorphine injections; b) providing addicted and nonaddicted animals a choice, under water-deprivation, of drinking water or I-G-2 both with and without distinguishing cues; c) training nonaddicted rats under water deprivation to press a lever in a Skinner-Box to obtain progressively increasing concentrations of I-G-2; d) comparing lever pressing of addicted and nonaddicted animals when working for I-G-2 and/or water when presented with distinguishing cues.

Patient Material: None

Major Findings. a) Rats showed no sign of discriminating I-G-2 from water even when the I-G-2 concentration was raised to 50-60 mcg/kg; nalorphine-precipitated abstinence signs were noted in a first (short term) study using a relatively low concentration of I-G-2 (5 mcg/kg); b) neither addicted nor nonaddicted rats distinguished I-G-2 from H_2O by taste, but findings in both suggested a conditioned preference on the basis of effect; c) high reliability was found in the Skinner Box work for counts of lap rate and lever-pressing with no indication that rats could taste I-G-2 in concentrations from 5 to 60 mcg/kg; d) when distinguishing cues were present, lever-pressing rates of addicted rats exceeded those of controls on water-deprivation days regardless of the fluid reward, while on water-satiation days rates of addicted rats were higher, but only when I-G-2 was the reward. Abstinence signs were more marked on water-satiation days.

Scientific Significance. From a clinical standpoint, the problem of "relapse" following cure has been the most difficult to comprehend and the least responsive to treatment. Although behavior of human addicts has long suggested that development of "physical dependence" permits drug-seeking behavior to become "conditioned," definitive tests of this hypothesis are possible only in animals. Positive results on the project may help to establish some variables of which "relapse" is a function and indicate new methods of prevention and treatment. The present studies indicate strongly that I-G-2 is a suitable drug for the described purposes. Its use in the behavioral studies provided very encouraging support for the stated psychopharmacogenic theory of addiction and relapse to opioids, and perhaps to alcohol.

Proposed Course of Project. The problems under immediate investigation, basic pharmacological and learning or conditioning studies, will be pursued through 1961. Pharmacological work will consist of developing and applying instruments for measuring precisely temperature changes, cardiac rate, oxygen consumption, and the recording of observational data during addiction and abstinence. These data, in addition to being informative per se, will be used to determine the peak of the abstinence syndrome and thus the optimal time for use of I-G-2 as a reward or reinforcer in the behavioral studies. The behavioral studies are being expanded both with regard to the number of animals and the measures necessary for defining preference for and "relapse" to the use of I-G-2. In cooperation with the Dept. of Pharmacology, University of Michigan, similar studies will be initiated on monkeys.

Part B included: Yes

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B. Honors, Awards, and Publications

Publications other than abstracts from this project:

1. Wikler, A., Green, P. C., Smith, H. D. and Pescor, F. T.: Use of a dilute aqueous solution (5 mcg/ml) of a benzimidazole derivative with potent morphine-like actions orally as a presumptive reinforcing agent of drug seeking behavior in the rat. Bull. Drug Addiction and Narcotics, p. 2244, app. 8, pp. 1-16. Min. 21st Meet., Committee on Drug Addiction and Narcotics, NRC. Washington, D. C. Natl. Acad. Sci. (Jan.) 1960.

2. Wikler, A.: Japanese translation of The Relation of Psychiatry to Pharmacology (Baltimore, Williams and Wilkins, 1957. pp. 322). Edited by a committee headed by Prof. H. Kumagai, Dept. Pharmacology, University of Tokyo, Tokyo, Japan. Iwanami Publishing Co., 1960. pp. 412.

Honors and Awards relating to this project:

Wikler, A.:

1. By invitation, delivered lecture on "Conditioning theory and relapse to narcotics," before British Society for Addiction, London, England, 18 October 1960.

2. By invitation, delivered lecture on "Tolerance, addiction and habituation," to staff and students, University of Manchester Medical School, Manchester, England, 20 October 1960.

Serial No. M-AR-9 (c) - 1
1. Addiction Research Center
2. Experimental Neuropsychiatry
3. PHS Hospital, Lexington, Ky.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Effects of Drugs and Other Variables on "Mental Set."

Principal Investigator: Abraham Wikler

Other Investigators: C. A. Haertzen

Cooperating Units: Clinical Division, PHS Hospital, Richard Chessick

Man Years (cal. yr. 1960):

Total:	2/3
Professional:	1/3
Other:	1/3

Patient Days (cal. yr. 1960): (by cooperating unit)

Project Description:

Objectives. To determine 1) the extent to which effects of the psychotomimetic drug LSD-25 on response set in nonpsychotic subjects resembles certain characteristics of schizophrenic patients, 2) the degree of specificity of LSD-25 in regard to the effects of non-psychotomimetic drugs (morphine, pentobarbital, amphetamine) and 3) the influence of fatigue on such sets in psychotic and non-psychotic subjects.

Methods Employed. The procedure described by Huston and Singer (Arch. Neurol. Psychiat. 53: 365-369, 1945) for measuring auditory-manual reaction time was modified for present purposes. The foreperiods, or the time between the warning signal and the signal to press a key, were maintained in the original 1) regular order of 3.5, 10.0, 5.0, 2.0, and 20.0 seconds, and 2) in randomized or irregular order. The two orders were given each subject on two separate days, in the present study, changing the sequence of "regular" and "irregular" orders to control for "time-action" of the drugs. The effects of placebo, LSD-25, morphine, pentobarbital, and amphetamine on such reaction times in non-psychotic patients were compared, and these results were in turn compared with similar data obtained from schizophrenic patients. The effects of fatigue were studied in both groups of subjects by measuring the effects of having the "regular" first, as opposed to having it follow the "irregular" order. Measures of fatigue were also obtained by changing the sequence of the 2.0- and the 3.5-second foreperiod.

Patient Material	No.	Average Stay (days)
Admissions:	--	--
Outpatients:	--	
No. of visits:	--	

Major Findings. Initial findings were presented in the previous annual report. The data showed that LSD-25, morphine, and pentobarbital slowed reaction times on both "regular" and "irregular" orders, reduced the mean separation of the two curves and shifted the optimal foreperiod from 2.0 to 3.5 seconds. Reaction time patterns under these drugs are similar to but not as marked as those found in schizophrenia. The gathering of additional data was completed and collated for processing by IBM-650 equipment in 1960. This work will be done by the Computing Center of the University of Kentucky and will entail various applications of analysis of variance and computing of t-tests.

Scientific Significance. The use of LSD-25 for producing experimental "models" of schizophrenia implies that this drug produces changes in some variables that are critically involved in production of the clinical disorder. Previously presented data suggest that "mental set" or response set as measured here is not one of these variables, since LSD-25 and certain non-psychotomimetic drugs produce similar alterations. Present data when analyzed will provide more clearly defined comparisons of "mental set" of schizophrenics and of post-addicts under LSD-25, morphine, pentobarbital, and amphetamine. Present data will also determine, at least partially, the extent to which the defect of "mental set" in schizophrenic patients is due to change in order of particular foreperiods and "fatigue."

Proposed Course of Project. Future work will be partly determined by the direction and significance found in the analyses described above. Attempts may be made to produce schizophrenic-like defects of "mental set" in normal subjects by non-pharmacological means, such as distracting or unexpected stimuli, or by non-injurious conditioning procedures. The effect of chronic administration of chlorpromazine in schizophrenic patients may also be studied.

Part B included: Yes

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B. Honors, Awards, and Publications

Publications other than abstracts from this project: None

Honors and Awards relating to this project:

Wikler, A.:

Presented seminar on "The effects of drugs on the central nervous system," Dept. of Physiology, Yale University Medical School, New Haven, Conn., 17 March 1960.

Serial No. M-CS-CM-1
1. Laboratory of Clinical Science
2. Section on Cerebral Metabolism
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Age changes in cerebral blood flow and metabolism in man.

Principal Investigator: Louis Sokoloff

Other Investigators: Seymour S. Kety

Cooperating Units: Section on Psychiatry, M-CS-Ps(C)-1; Laboratory of Socio-Environmental Studies, M-S-D-4; Section on Aging, Laboratory of Psychology, M-P-A-3.

Man Years (calendar year 1960):		Patient Days (calendar year 1960):
Total:	0.25	None
Professional:	0.25	
Other:	None	

Project Description:

Objectives: Numerous previous studies have demonstrated a decline in cerebral blood flow and metabolic rate with age. Most of these studies failed to give evidence of adequate control of the effects of disease states frequently associated with aging. The objective of this study is to determine the effects of aging per se on cerebral circulatory and metabolic functions independent of the effects of associated disease. Also as part of a broad, multidisciplinary project on aging, possible correlations between changes in cerebral circulatory and metabolic functions with those in psychological and mental functions observed in old age are being investigated.

Methods Employed: The basic method employed in all these studies is the nitrous oxide method for the estimation of cerebral blood flow and metabolism in man.

Major Findings: Studies in over 50 normal elderly men carefully selected for their relative freedom from the common degenerative diseases of old age and who were functioning more or less normally in their communities have demonstrated that

Project Description (continued):

there are no reductions in cerebral blood flow and oxygen consumption as a result of chronological or physiological aging per se. The presence of hypertension in otherwise normal elderly people does not alter this picture. On the other hand, in the presence of arteriosclerosis, even when it is so minimal as to be asymptomatic, there is a definite reduction in cerebral blood flow and a reduction in the oxygen tension of the cerebral venous blood and, therefore, probably also of the cerebral tissues, indicating the existence of a relative cerebral anoxia. Cerebral blood flow and cerebral venous pO_2 in patients with chronic brain syndrome and psychosis were no lower than in the asymptomatic arteriosclerotic subjects, but they differed in that their cerebral extraction from the blood was reduced so that their cerebral oxygen consumption was markedly lowered. These results suggest that it is arteriosclerosis rather than chronological age that is responsible for the fall in cerebral blood flow and oxygen consumption so often observed in elderly subjects and that the primary change is cerebral circulatory insufficiency and cerebral anoxia. It is probable that the reduction in cerebral metabolic rate results from tissue damage caused by a prolonged period of cerebral anoxia, and it is possible that the clinical picture of chronic brain syndrome is the ultimate consequence of the effects of this cerebral anoxia.

Significance to Bio-medical Research and the Program of the Institute: Deterioration in mental and psychological functions is a major accompaniment of the aging process. It is hoped that the results of these studies may lead to a better understanding of some of the biological changes which may be causative or contributory to the deterioration in cerebral functions in the aged.

Proposed Course of Project: No further experimental work in this project is anticipated. The data already accumulated has been processed, organized, and a manuscript on this work has been prepared for publication. It is to be included in the forthcoming monograph on the multidisciplinary NIMH project on aging which is currently in preparation. Current work on this project is confined entirely to editorial work on the monograph.

Part B included: Yes

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B: Honors, Awards, and Publications

Publication other than abstracts from this project:

1. Sokoloff, L.: Quantitative measurement of cerebral blood flow in man. Methods in Medical Research VIII, 253-261, 1960.

2. Lewis, B.M., Sokoloff, L., Wechsler, R.L., Wentz, W.B., and Kety, S.S.: A method for the continuous measurement of cerebral blood flow in man by means of radioactive krypton (Kr^{79}). J. Clin. Invest., 39: 707-716, 1960.

3. Sokoloff, L. and Kety, S.S.: Regulation of cerebral circulation. Physiol. Rev., 40: 38-44, 1960.

4. Sokoloff, L.: The central nervous system metabolism in vivo. Handbook of Physiology. American Physiological Society, Washington, D. C., 1960 (in press).

5. McKhann, G.M., Albers, R.W., Sokoloff, L., Mickelsen, O., and Tower, D.B.: The quantitative significance of the γ-aminobutyric acid pathway in cerebral oxidative metabolism. Conference on Inhibition of the Nervous System and γ-Aminobutyric Acid. Pergamon Press, London, 1960 (pp. 169-181).

6. Dastur, D.K., Lane, M.H., Hansen, D.B., Kety, S.S., Butler, R.N., Perlin, S., and Sokoloff, L.: Effects of aging on cerebral circulation and metabolism in man. Biological and Behavioral Aspects of Normal Aging in Man. NIMH Monograph. U.S. Government Printing Office (in press).

7. Sokoloff, L.: Local cerebral circulation at rest and during altered cerebral activity induced by anesthesia or visual stimulation. The Regional Chemistry, Physiology and Pharmacology of the Nervous System. S.S. Kety, Editor. (in press).

8. Sokoloff, L.: The effects of carbon dioxide on the cerebral circulation. Anesthesiology (in press).

Honors and Awards relating to this project: None

Serial No. M-CS-CM-4
1. Laboratory of Clinical Science
2. Section on Cerebral Metabolism
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: The mechanism of action of thyroxine and its relation to cerebral metabolism.

Principal Investigator: Louis Sokoloff

Other Investigators: Seymour Kaufman, William P. Weiss

Cooperating Units: Laboratory of Cellular Pharmacology, NIMH Serial No. M-CP-7

Man Years (calendar year 1960):		Patient Days (calendar year 1960):
Total:	4.75	None
Professional:	1.75	
Other:	3.00	

Project Description:

Objectives: The ultimate objective of this project is the determination of the unique features of cerebral metabolism which render the mature brain independent of the circulating blood level of thyroid hormone. An intermediate objective, and probably a necessary step in order to attain the ultimate objective, is the determination of the mechanism of the physiological action of the thyroid hormone. In pursuit of this intermediate objective, the role of thyroxine in the regulation of protein synthesis and turnover is under investigation.

Methods Employed: The effect of thyroxine on the rate of incorporation of a radioactive amino acid (DL-Leucine-1-C^{14}) into protein is studied in a completely *in vitro* system containing an actively phosphorylating mitochondrial system and a microsomal enzyme system. The mitochondrial system supplies the energy and the microsomal system the enzymes necessary for the *in vitro* synthesis of proteins.

Project Description (continued):

Major Findings: Earlier studies in this project have demonstrated that thyroxine penetrates the blood-brain barrier sufficiently well for a sustained increase in circulating thyroxine to be reflected in the brain tissue; the lack of thyroxine effect on the oxidative metabolism of the mature brain cannot, therefore, be attributed to the blood-brain barrier. More recent studies have demonstrated that thyroxine, administered *in vivo* or *in vitro*, stimulates the *in vitro* incorporation of amino acids into protein, and therefore, probably also protein biosynthesis. This effect of thyroxine has been found to be localized in the mitochondrial fraction. Graded increasing effects are observed with increasing concentrations of thyroxine between 10^{-7}M and 10^{-4}M. At 10^{-3}M, thyroxine inhibits amino acid incorporation and uncouples oxidative phosphorylation indicating that the uncoupling effect of thyroxine is a qualitatively different one observed only at higher or toxic concentrations. The possibility that this thyroxine effect might be a preservative one rather than a true stimulation has been excluded by the results of complete time course studies. It has also been found that there is a 5 minute latent period of action of the thyroxine, when added *in vitro*, which is followed by a finite 25 minute period of stimulation. These results suggest that during the latent period an intermediate is formed which is then used up during the period of stimulation. The formation of the unknown intermediate during the lag period has been found to be dependent on the presence of an active oxidative phosphorylating system. During the past year it has been demonstrated that phosphorylation derived from glycolytic processes cannot substitute for oxidative phosphorylation. Mitochondria are, therefore, essential for the thyroxine effect, but the effect is to stimulate amino acid incorporation into microsomal protein. The identity of the intermediate or the nature of the chemical transformation occurring during the latent period which led to the subsequent stimulation of amino acid incorporation into protein have not yet been elucidated, but studies aimed at this goal are currently in progress.

In order to evaluate the possible relationship of this laboratory effect of L-thyroxine to its true physiological effect, comparative studies of the effects of analogues of L-thyroxine were undertaken. It has been found that D-thyroxine, a physiologically less active optical isomer of L-thyroxine, is equally effective as L-thyroxine when added *in vitro* to the cell-free homogenate used in these studies, but when injected into the animal, it fails to stimulate the amino acid incorporation into protein as does the L-isomer. This result suggests that D-thyroxine is potentially capable of acting intra-cellularly

Project Description (continued):

like L-thyroxine but is physiologically less active because it does not get to the appropriate enzyme sites within the cells, (perhaps, because of more rapid excretion or inability to penetrate the cell membranes). L-triiodothyronine, a physiologically potent analogue of L-thyroxine, has been found to stimulate amino acid incorporation as effectively as the natural hormone when injected *in vivo*, but consistent effects have not yet been obtained with it *in vitro*.

The studies of the relative effects of thyroxine analogues have recently been extended to a variety of derivatives with varying degrees of iodination of the rings. The results of these studies indicate that the order of activity is as follows: tetraiodo > triiodo > diiodo > no iodine, and the order with respect to the side chain is acetic > propionic > alanine. Tetraiodothyroacetic acid has been found to be the most active of the compounds studied, including L-thyroxine. These results are consistent with the physiological activities of these analogues.

It has long been known that salicylates in large doses exert thyroxine-like effects on gross body metabolism. This phenomenon has recently been studied in this laboratory, and it has been found that like thyroxine, salicylates also stimulate amino acid incorporation into protein. It has not yet been determined, however, whether this is an independent thyroxine-like action of salicylates or the result of its release of endogenous thyroxine from binding on protein.

If the thyroxine effect under study in this project reflected a true tonic physiological action of the thyroid hormone, then it might be expected that hypothyroidism would result in a reduced rate of protein synthesis. Studies on thyroidectomized animals have been carried out during the past year, and it has been found that thyroidectomy does indeed result in a reduced rate of amino acid incorporation into protein.

Recently, the studies have been extended to the action of thyroxine on amino acid incorporation into protein in homogenates derived from brain tissue. It has been found that in young adult rat brains, thyroxine does not stimulate and may even inhibit amino acid incorporation into protein. However, in 15-20 day old rats, in which brain growth and development are still proceeding rapidly, thyroxine does stimulate the rate of amino acid incorporation. These effects of thyroxine parallel those which have been observed on the cerebral oxygen consumption in animals and man.

Project Description (continued):

Significance to Bio-medical Research and Mental Health Program: A unique feature of the cerebral metabolism is its apparent lack of response to high circulating levels of thyroid hormone. An understanding of the basis of this unique behavior may reveal information concerning the metabolism of the brain in health and disease. Also, the mechanism of action of thyroxine has been under investigation for many decades, but thus far a satisfactory explanation of the mechanism by which it increases metabolic rate, stimulates metamorphosis and growth, or causes the many disturbances in body physiology and biochemistry in thyroid disease has eluded investigators. The solution of this problem could then lead to fundamental advances not only in the understanding of how this important hormone regulates bodily functions but also of the nature of bodily processes on which it acts.

Proposed Course of Project: Two paths of investigation will be followed in this project. Further efforts will be made to evaluate the relationship of the thyroxine effect found in this project to the true physiological effect of thyroxine. This may require the development of techniques to study the effect entirely *in vivo*. The other path will be directed at a clear elucidation of the biochemical mechanisms through which thyroxine stimulates protein synthesis. In contrast, to the first path, this one may require further simplification of the system, perhaps, to the point of isolating *in vitro* the single reaction on which the thyroxine effect is exerted. The immediate question to be investigated is which of the several known steps involved in the incorporation of amino acids into protein is the one stimulated by thyroxine.

Part B included: Yes

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B: Honors, Awards, and Publications

Publications other than abstracts from this project:

1. Cochin, J. and Sokoloff, L.: Effects of administration of L-thyroxin on liver N-demethylating activity in normal and morphine-treated rats. Proc. Soc. Exp. Biol. Med., 104: 504-506, 1960.

2. Sokoloff, L.: Studies on the peripheral action of thyroxine and its relation to cerebral metabolism. Chemical Pathology of the Nervous System, J. Folch-Pi, Editor. Pergamon Press, London, 1960 (in press).

3. Sokoloff, L. and Kaufman, S.: Thyroxine stimulation of amino acid incorporation into protein. J. Biol. Chem. (in press).

Honors and Awards relating to this project: None

Serial No. M-CS-B-1
1. Laboratory of Clin.Science
2. Section on Biochemistry
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Fractionation of brain constituents. Isolation and identification of antigen responsible for production of experimental allergic encephalomyelitis (EAE).

Principal Investigator: Marian W. Kies

Other Investigators: Spencer Gordon, Robert Laatsch, Ellsworth C. Alvord, Jr.

Cooperating Units: NINDB Laboratory of Neuroanatomical Sciences
University of Washington Medical School, Seattle, Washington

Man Years: (calendar year 1960)
Total: 1 1/2
Professional: 1/2
Other: 1

Patient Days (calendar year 1960)
None

Project Description:

Objectives: Isolation and characterization of the protein in brain responsible for the allergic demyelinating process - study of the relationship of individual neural proteins to various neurologic and psychopathologic disorders.

Methods Employed: Fractionation of brain and spinal cord by classical biochemical procedures. Bioassay of the various fractions in the guinea pig for encephalitogenic activity. Electrophoretic analysis of the various protein fractions isolated. Ultracentrifugal fractionation of whole brain to determine the cellular localization of the antigen.

Major Findings: The highly antigenic water soluble protein fraction isolated from acid extracts of defatted guinea pig brain has been further fractionated by chromatography on DEAE and CM-cellulose columns. CM-cellulose, which is a cationic exchanger, proved to be

most useful for purification. The active protein is adsorbed on CM-cellulose from 0.005 M acetate (pH5) leaving other inert proteins in solution. The most highly purified fraction yet obtained can be removed from the CM-cellulose with 0.25 M NaCl. This protein is similar to the borate-soluble fraction reported previously, has an isoelectric point of 10.5, a molecular weight of approximately 20,000 and appears to contain only one component by the ultracentrifugal analysis. Its encephalitogenic activity is detectable at 2 mcg but not at 0.8 mcg. Although the specific activity of this preparation is not significantly higher by the present bioassay procedure, its chemical purity is superior to that of the water-soluble fraction from which it was prepared (judged by its behavior on CMC columns, electrophoretic behavior, isoelectric turbidity measurements etc.). When a sufficient quantity is available this fraction will be used for the final definitive studies on suppression - cross reactivity with active proteins from other species and with other neural proteins from the homologous source.

Fractionation of bovine cord and rat brain are underway at the present time. Rat brain contains less activity per mg than guinea pig brain and the water-soluble protein isolated from the acid extract of defatted brain has lower specific activity than the corresponding guinea pig preparation.

Dr. Roboz has reported the isolation of a KCl soluble protein from bovine cord which may have comparable specific activity to the guinea pig encephalitogen. This material does not account for all of the activity present in cord and it has been observed by our group that extraction of the KCl residue by dilute acid (our extraction procedure) yields more soluble active protein. Both of these extracts can be further purified by chromatography on CM-cellulose. It is not known at present whether the two extracts are chemically alike or not.

Although it is generally agreed that the antigenic activity of brain is related to the myelin because of the peculiar susceptibility of myelin to destruction during the disease process, the experimental proof of this was lacking (or questionable).

One group has claimed that the activity was associated with the mitochondria whereas another group presented rather inconclusive evidence that the activity was in axonal fragments rather than glial cells. Both groups used inadequate ultracentrifuge procedures and in each case the bioassay was not quantitative.

Considerable attention has been devoted in our laboratory to the problem of isolating myelin from the soluble supernatant fraction, mitochondria, microsomes and nuclei in order to settle this question definitively. This was not a simple problem technically. Although many biochemists apply standard (liver) centrifugation procedures empirically to brain, it is easy to demonstrate by electron microscopic techniques that the "nuclear fraction," the "mitochondrial fraction" etc. are all grossly contaminated with myelin. We have obtained a fairly pure myelin fraction by density gradient centrifugation rather than differential speed centrifugation. Centrifuge tubes are partially filled with 30% sucrose brain homogenate and then completely filled with 8.5% sucrose (so that 2 distinct layers are formed). Mitochondria, nuclei and larger microsomes are sufficiently dense to sediment in 30% sucrose and the myelin collects at the interface.

A washed preparation of myelin isolated in this manner showed very little mitochondrial contamination (in electron micorgraphs or by succinoxidase assay). Bioassay of EAE activity showed that the myelin had a higher specific activity than whole brain and that the pellet (containing mitochondria, nuclei, and possibly microsomes) contained little or no activity. The soluble supernatant fraction was inactive.

A protein fraction, similar to one prepared from whole brain, has been isolated from the myelin prepared by ultracentrifugation. This protein has an isoelectric point of 10.5, is similar to the whole brain preparation in its behavior on electrophoresis, and has encephalitogenic potency of the same order of magnitude.

Significance to Mental Health Research: This project, like the companion project on immunological aspects of EAE was undertaken to yield information on the basic mechanisms underlying a neurological syndrome due to tissue autosensitivity. Brain damage, in this case can be detected readily both from neurological signs and histological evidence. It is conceivable that sensitization to other brain proteins might cause more subtle changes, e.g., those leading to psychoses. Enzyme levels in the brain might be influenced by an "allergic" reaction to a specific protein. Hypertrophy or atrophy of specialized areas might also be controlled by such mechanisms.

The information gained is also of significance in the field of comparative neurochemistry - the similarities and differences in the chemical composition of brains of different species.

Proposed course of project: Further studies on the chemical and immunological specificity of encephalitogenic proteins are in progress. Species specificity will be more carefully defined (if, in fact, it exists).

The myelin studies will be continued to extend our knowledge of the structure and function of this important neural constituent. Enzymatic activities related to the protein in developing myelin will be studied.

Part B included: No

Serial No. M-CS-B-2
1. Laboratory of Clinical Science
2. Section on Biochemistry
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Immunological studies on experimental allergic encephalomyelitis (EAE).

Principal Investigator: Marian W. Kies

Other Investigators: Peter Mueller and Ellsworth C. Alvord, Jr.

Cooperating Units: Unit on Psychosomatics; University of Washington Medical School, Seattle, Washington.

Man Years (calendar year 1960)	Patient Days (Calendar Year 1960)
Total: 2	
Professional: 1/2	None
Other: 1 1/2	

Project Description:

Objectives: Investigation of the immunological aspects of allergic encephalomyelitis; application of these results to a study of the pathogenesis of the experimental disease.

Methods employed: (A) Use of purified antigen for immunologic studies on animals injected with CNS material plus adjuvant.

(B) Study of the effects of dietary deficiency on disease induction.

(C) Investigation of adjuvant effect.

Major findings: (A) Suppression of EAE by purified antigen: Previously we reported that purified brain protein fractions which induce the disease when injected with adjuvant also suppress clinical signs of disease when injected intracutaneously in saline 8-18 days after disease induction. During the past year, knowledge of this phenomenon has been extended as follows:

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A. (Project Description continued)

1. Time relationships of suppression treatment: Pretreatment which was begun either 45 days before challenge or 10 days before challenge was more effective than suppression injections which were started a week after challenge. This was true whether EAE was induced with a massive "challenge" (2.5 mg whole cord) or with a barely maximal "challenge" (0.02 mg purified antigen). When massive "challenge" is given the inhibiting effects of purified antigen are recognized by a delay in disease onset from 11-12 days for the controls to 16-17 days for the "EAE inhibited" group and a reduction in mortality from 99% of the controls in 20 days to 70% of the treated animals in 30 days. "Suppression" or inhibition of a barely maximal challenge completely prevents development of clinical (neurological) signs of disease and inhibits more or less completely the histological damage.

2. Route of injection and vehicle: Intravenous injections of saline solutions appear to be as effective as intradermal injections but the incorporation of incomplete adjuvant in the intradermal injections markedly increases the effectiveness of the latter. (Incomplete adjuvant consists of a water-in-oil emulsion of mineral oil and aquaphor, a hydrophilic emulsifying agent).

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A. (Project Description continued)

Effect of Injection Technique On Suppression of EAE[1]
(Barely Maximal Challenge)

Injection	Disease Index ± S. E. Mean		
Amount, Route, Vehicle	Treated Series		Control Series
3 mg, I.D. (saline)	0.7 ± 0.2	($p = 0.01$)	6.7 ± 1.7
3 mg, I.V. (saline)	2.1 ± 0.9	($p < 0.01$)	9.0 ± 0.5
0.3 mg, I.D. (saline)	5.0 ± 1.7	($p = 0.05$)	9.3 ± 0.2
0.3 mg, I.D. (oil/aquaphor)	0.8 ± 0.7	($p < 0.01$)	9.3 ± 0.2

[1] These data are incomplete in so far as establishing the lower limit of effectiveness of the oil/aquaphor injection. In the "massive challenge" technique referred to above as little as 0.003 mg injected I.D. in oil/aquaphor appeared to be as effective as 3 mg in delaying the average day of onset of neurological signs.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A. (Project Description continued)

3. Specificity of the suppression effect: Purified encephalitogenic protein from brain suppresses disease induced by the fraction itself, by whole homologous brain, or by whole heterologous cord. Brain protein fractions which are not encephalitogenic have not shown any suppressive effect. Non-neural proteins (e.g. egg albumen and PPD) are also ineffective.

(B) Effect of diet on EAE induction in guinea pigs: In collaboration with Dr. Peter Mueller we have investigated the plasma "free fatty acid" (FFA) concentration in guinea pigs made encephalitic with whole bovine cord and adjuvant. This study was related to an earlier investigation on lipemia in EAE published by our group. Those guinea pigs with lipemic plasma also had elevated FFA values, but more importantly many not showing visible lipemia had higher than normal FFA values.

Since normal guinea pigs have increased plasma FFA values after fasting, the possibility of starvation effects in very sick animals had to be ruled out. Dr. Mueller had observed in another study that scorbutic animals do not react to fasting by elevation of FFA. This suggested an experimental means of testing the effect of starvation on the plasma FFA values of paralyzed guinea pigs. The development of allergic encephalomyelitis in 12 scorbutic guinea pigs was compared with that in 12 animals on the same diet supplemented with vitamin C. Neurological signs in the scorbutic animals were difficult to assess. Two animals were sacrificed on day 17 because of acute illness, but their worsened condition apparently resulted from vitamin C deficiency rather than encephalitis (only one of the 12 scorbutic animals showed histological evidence of EAE). In contrast, 11 out of the 12 animals receiving vitamin C supplements were positive histologically and 8 out of the 12 were acutely paralyzed by the 18th day. All remaining animals in both series were sacrificed on the 21st day. Since the scorbutic animals failed to

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Part A. (Project Description continued)

succumb to EAE, their FFA values were not significantly different from a previous series of scorbutic guinea pigs. The EAE animals, on the other hand, again showed elevated plasma FFA values.

These results were entirely unexpected and shifted our attention from the effect of fasting on FFA values to the question of how a specific dietary deficiency could prevent brain damage by the autosensitization reaction.

(C) Investigation of adjuvant effect: Further studies have been carried out on the quantitative relationship between the adjuvant (killed mycobacteria) and CNS antigen required for disease induction. A minimum amount of whole CNS or fraction is necessary to induce neurological damage (0.05 mg. lyophilized bovine cord, 0.05-0.1 mg lyophilized guinea pig brain, 1-5 mcg purified protein). These small amounts of CNS are more effective when combined with small amounts of adjuvant and can be completely inhibited by larger amounts. Conversely large amounts of CNS require large amounts of adjuvant for maximal effect. The effective concentration range of adjuvant is 0.02-2 mg. Above this range, even excessive amounts of whole CNS (> 2.5 mg) fail to overcome the inhibitory affects of the mycobacterium.

Previous studies in this laboratory had demonstrated that preinjection of mycobacterium prevented EAE. It has now been shown that injection of 0.1 mg mycobacterium in oil/aquaphor 8, 13 and 18 days after the "challenge" injection also inhibits both clinical and histological signs of disease.

Significance to Mental Health Research: The human diseases most closely related to EAE in their pathogenesis are multiple sclerosis and the post-infectious or post-vaccinal encephalitides. All of the major findings reported this year on the immunological aspects of EAE have to do with various means of preventing development of the experimental disease. Ultimately one or a combination of these

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Part A. (Project Description continued)

might prove to be of clinical value in the related human diseases. As a problem in mental health, damage to the central nervous system is of great concern to our group; on the other hand, the results are not limited to mental health. The possibility of prevention or treatment is also of great importance to other tissue autosensitization diseases such as thyroiditis, adrenalitis, lupus, and aspermatogenesis.

The effect of dietary deficiency on immunologic reactions has not been clarified. Vitamin C is thought to be of importance in metabolic reactions of the white cells and the ascorbic acid deficiency may be depressing leucocyte formation to such an extent that tissue antibody production is prevented.

Elucidation of the adjuvant effect is basic to many problems in experimental immunology. The adjuvant has been used empirically to increase antibody formation, prolong the period of high antibody titer, and enhance delayed hypersensitivity reactions but its function has never been clarified.

Proposed course of the project: Immediate plans for the future involve attempts to differentiate more clearly between encephalitogen-induced suppression of the disease and adjuvant-induced suppression. Further studies on simultaneous injection of CNS and adjuvant emulsions are in progress

The study of the effects of dietary deficiency is being extended to include: a) Influence of the scorbutic diet on other effects of the adjuvant - i. e. the positive skin test obtained with PPD. It may be that the effect of ascorbic acid deficiency of EAE is related to its suppression of the adjuvant reaction rather than to a direct influence on brain damage. b) Effect of the diet on another typical autosensitivity reaction (aspermatogenesis). c) Effect of other vitamin deficiencies on EAE. (Some years ago it was pointed out by Lee, et al, at

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Part A. (Project Description continued)

Rockefeller Institute that BSVS mice on a fox chow, bread and milk diet were 100% susceptible to EAE whereas the same strain on a simplified synthetic diet lacking folic acid, B_{12} and biotin were only 10% susceptible. The 100% susceptibility to EAE was restored by adequate supplementation of the diet. Their interest was in genetic specificity and to my knowledge the dietary aspects of the problem were not further investigated. Whether or not the different vitamin deficiencies in different strains of animals are related remains to be seen.

Part B included: Yes

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Calendar Year 1960

Part B. Honors, Awards and Publications

Publications other than abstracts from this project:

Shaw, C-M., Fahlberg, W. J., Kies, M. W. and Alvord, E. C., Jr. Suppression of experimental "allergic" encephalomyelitis in guinea pigs by encephalitogenic proteins extracted from homologous brain. J. Exp. Med. 111:171-180, 1960.

Kies, M. W., Shaw, C-M., Fahlberg, W. J., Alvord, E. C., Jr. Factors affecting the suppression of allergic encephalomyelitis by homologous brain protein fractions. Annals of Allergy 18:849-858, 1960.

Serial No. M-CS-B-5
1. Laboratory of Clinical Science
2. Section on Biochemistry
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Metabolism of histidine

Principal Investigator: Marian W. Kies

Other Investigators: None

Cooperating Units: None

Man Years (calendar year 1960)	Patient Days (Calendar Year 1960)
Total: 1 1/2	None
Professional: 1/2	
Other: 1	

Project Description:

Objectives: To study the intermediary metabolism of histidine, specifically the conversion of imidazolone propionic acid to formiminoglutamic acid.

Methods employed: Classical protein purification techniques have been applied to liver homogenates to obtain a partially purified imidazolone propionic acid hydrolase. The enzyme has been characterized with respect to its pH optimum, inhibitors, K_m value, etc.

Major findings: Histidine is converted in animal tissues to many different compounds; in mammals one of the most interesting pathways of its metabolism is through urocanic acid. Urocanase converts urocanic acid to imidazolone propionic acid (IPA) an extremely unstable compound, which was stabilized and characterized last year by Dr. Brown. He showed by means of radioactive tracer techniques that IPA is converted anaerobically by tissue homogenates to formiminoglutamic acid (FGA) and aerobically to hydantoin propionic acid (HPA). The formation of formyl isoglutamine (FIG) from IPA is non-enzymatic and occurs spontaneously at pH 7.4 in air. To avoid FIG

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Part A. (Project Description continued)

formation, assays of the enzyme which converts IPA to FGA had to be carried out anaerobically. The enzyme has been purified 60-fold and under proper conditions it will catalyze the conversion of IPA to FGA almost 100%. The purified enzyme is free of urocanase activity and is not inhibited by hydroxylamine and semicarbazide which are potent inhibitors of urocanase action. Imidazolone propionic acid hydrolase is completely inhibited by p-chloromercuribenzoate a reagent which is known to combine with protein sulfhydryl groups.

Although the existence of this enzyme had been postulated and the formation of FGA from IPA demonstrated experimentally, this is the first time IPA (isolated from the urocanic acid:urocanase reaction mixture) has been converted by a purified hydrolase enclusively to FGA and the isolated system studied.

Significance to Mental Health Research: This unit of work was a continuation of a project started with Dr. Brown to study schizophrenic and normal human metabolism of histidine. It is an additional contribution to our knowledge of the mammalian metabolism of histidine. The enzyme studied is a link in the conversion of histidine to glutamic acid, an amino acid which occupies an important position in brain metabolic reactions.

Proposed course of project: No further studies are contemplated at the present time.

Part B. included Yes

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Part B. Honors, Awards and Publications

Publications other than abstracts from this project:

Brown, D. D., Tomchick, R. and Axelrod, J. The distribution and properties of a histamine methylating enzyme. J. Biol. Chem. 234:11, 1959.

Brown, D. D. and Kies, M. W. The mammalian metabolism of L- histidine. I. The enzymatic formation of L- hydantoin-5-propionic acid. J. Biol. Chem. 234:3182-3187, 1959.

Brown, D. D. and Kies, M. W. The mammalian metabolism of L- histidine. II. The enzymatic formation, stabilization, purification and properties of 4(5)-imidazolone-5(4)-propionic acid, the product of urocanase activity. J. Biol. Chem. 234:3188-3191, 1959.

Brown, D. D., Silva, O. L., McDonald, P. B., Snyder, S. R. and Kies, M. W. The mammalian metabolism of L- histidine. III. The urinary metabolites of L- histidine-C^{14} in the monkey, human and rat. J. Biol. Chem. 235: 154-159, 1960.

Brown, D. D., Silva, O. L. and McDonald, P. B. A comparison of the urinary metabolites of L- histidine-C^{14} in schizophrenic and normal subjects. J. Psychiatric Res. in press.

Serial No. M-CS-B-6
1. Laboratory of Clinical Science
2. Section on Biochemistry
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Intermediary metabolism of central nervous system.

Principal Investigator: Shoichi S. Hotta

Other Investigators: Marian W. Kies

Cooperating Units: None

Man Years (calendar year 1960)		Patient Days (calendar year 1960)
Total:	1	
Professional:	1/2	None
Other:	1/2	

Project Description:

Objectives: To investigate the metabolism of tyrosine and the effects of drugs thereupon.

Methods employed: A. Isolation of enzyme systems by standard techniques.

B. Incubation of C^{14} and H^{3} labelled compounds with enzyme preparations and isolation of metabolites.

C. Observation of biological effects of administration of metabolites to normal laboratory animals.

D. Administering some known drugs affecting CNS function *in vivo* and *in vitro* and determining effects on some metabolic processes.

Major findings: A. N-Methylation of tyramine by brain preparations has been observed under certain conditions. Isolation of N-methyl or N,N-dimethyl tyramine from normal rabbit, guinea pig, or rat brain was unsuccessful.

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Part A. (Project Description continued)

B. The p-hydroxyphenylpyruvate oxidase enzyme system has been partially purified. There is some indication that there are at least two difficultly separable enzymes involved. Catalase may be an integral part of the enzyme system.

Significance to Mental Health Research: Elucidation of the intermediary metabolism occurring in normal central nervous systems may afford means of understanding the abnormalities linked to mental deficiency.

Monoamines have been noted to exert physiological effects which appear to be mediated, in part, by way of the central nervous system. Tyramine, the monoamine related to tyrosine, has some of these typical biological effects.

Tertiary amines have been noted to have various CNS effects of great interest; i.e. LSD, chloropromazine, etc. N-methylated tyramine may also have some central nervous system effects. If N-methylated tyramine should have pschotic effects, this compound could conceivably be an abnormal metabolite in schizophrenia, partially responsible for the illness. Since the occurrence of N-methylated tyramine could not be demonstrated in normal laboratory animal brains, it may be that normally monoamine oxidase can rapidly oxidize any N-methylated tyramine formed. In mental illness this process may be functioning improperly leading to an accumulation of this tertiary amine.

Proposed course of project: A. Extract brains of laboratory animals and attempt to isolate and identify some tyrosine metabolites.

B. Isolation of enzyme systems from brain and liver and study influence of some psychomotor drugs on these systems.

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Part A. (Project Description continued)

C. Injection of N-methylated tyramine to observe the biological effects in laboratory animals.

D. Injection of monoamine oxidase inhibitors to laboratory animals, isolating the brain tissue and analyzing for methylated tyramine. This will be done with simultaneous injection of C^{14} tyrosine, tyramine or phenylalanine.

Part B included: No

Serial No. M-CS-B-7
1. Laboratory of Clinical Science
2. Section on Biochemistry
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Carbohydrate metabolism of central nervous system.

Principal Investigator: Shoichi S. Hotta

Other Investigators: Marian W. Kies

Cooperating Units: None

Man Years (calendar year 1960)		Patient Days (calendar year 1960)
Total:	1	
Professional:	1/2	None
Other:	1/2	

Project Description:

Objectives: To investigate the various controls existing in biological systems on the metabolism of carbohydrates.

Methods employed: A. Mincing whole brain tissues, homogenizing and fractionating the various subcellular fractions of brain by standard techniques and other techniques developed in our laboratories.

B. Incubation of C^{14} labelled compounds with the brain preparations and determining the distribution in various compounds by standard chemical techniques.

C. Determination of the effect of biological compounds, hormones, and psychomotor drugs on this distribution.

D. Administration of the effective compounds to animals to observe any biological effects.

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Part A. (Project Description continued)

Major findings: A. In an *in vitro* system, brain mince was found to convert an appreciable amount of glucose utilized to lactic acid in a completely aerobic atmosphere.

B. The addition of oxalacetate was found to increase the relative proportion of glucose converted to lactate, without interference in the conversion of glucose to carbon dioxide. Alpha ketoglutarate or succinate was found to reverse the effects of oxalacetate in part.

C. Addition of triphosphopyridine nucleotide demonstrated a very active hexose monophosphate shunt pathway for the utilization of glucose in the brain mince.

D. Insulin significantly increased the amount of glucose oxidized by both the hexose monophosphate shunt and Embden-Meyerhof pathways in brain mince preparation.

Significance to Mental Health Research: Brain tissue has been noted for its uniqueness in utilizing glucose as its major source of energy. It has been thought that mental illness is a reflection of some aberration in the energy relationships occurring in the brain. Thus it would appear that some internal control of the metabolism of carbohydrates may not be functioning properly in the mentally disturbed.

Oxalacetate has been noted to be a potent inhibitor of succinic dehydrogenase, an enzyme of the tricarboxglic acid cycle, and that this inhibition is reversible by succinate. Since brain tissue is a highly aerobic tissue, it seems significant that oxalacetate levels are high in brain tissue. It is important to study the effect of oxalacetate on the utilization of glucose in view of the primary role of glucose and the TCA cycle in brain tissue metabolism.

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Part A. (Project Description continued)

Insulin shock has been used in psychiatric treatment. Although there is evidence that insulin does not affect the A-V difference in glucose as regards the brain, in vivo, this hormone may play a significant role in the intracellular metabolism of brain tissue if it can cross the blood-brain barrier. This may occur in an abnormal situation such as mental illness, and the beneficial results of insulin treatment may not be wholly due to the lowering of blood glucose.

Proposed course of project: A. Brain minces, homogenates, and subcellular fractions will be incubated with C^{14} labelled substrates and the distribution into various fractions will be determined.

B. Attempts will be made to elucidate the effects of addition of various compounds, including hormones and psychomotor drugs, on this metabolism.

C. Effective compounds will be administered to laboratory animals to observe any biological effects, with a final assay done on isolated tissues.

Part B included: No

Serial No. M-CS-Ph-1
1. Laboratory of Clin.Science
2. Section on Pharmacology
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Biochemical factors involved in the action of drugs. II. Effect of drugs on the metabolism of adrenaline and other amines.

Principal Investigator: Julius Axelrod

Other Investigators: G.L. Whitby, G. Hertting

Cooperating Units: None

Man Years (calendar year 1960)	Patient Days (calendar year 1960)
Total: 1 1/2	None
Professional: 1	
Other: 1/2	

Project Description:

Objectives: To study the action of psychotropic drugs and other compounds on the metabolism of adrenaline, and to elucidate the role of catechol-O-methyl transferase in the inactivation of catecholamine hormones.

Methods Employed: General biochemical and pharmacological procedures.

Major Findings: Pretreating cats with pyrogallol, a catechol-O-methyl transferase inhibitor resulted in an elevation in the concentration of administered H^3 noradrenaline and decreased the level of H^3 norepinephrine in several tissues. Monoamine oxidase inhibitors had little or no effect on tissue H^3 noradrenaline but raised the levels of H^3 normetanephrine.

Psychotropic and adrenergic agents such as chlorpromazine, imipramine, reserpine, amphetamine, tyramine, guanethidine, cocaine, and Dibenzyline markedly reduced the uptake of administered H^3 noradrenaline in heart, spleen and adrenal gland and elevated the levels of the catecholamine in the blood. Phenobarbital,

dichlorisoproterinol, ouabain, iproniazid and JB516 did not affect the uptake of the catecholamine.

Chronic denervation of the superior cervical ganglia resulted in a marked impairment in the uptake of H^3 noradrenaline in the denervated organs.

Significance to Mental Health Research: It is hoped that information obtained from these investigations might explain some of the actions of psychotropic drugs and establish the normal role of catechol-O-methyl transferase.

Proposed course of project: The effect of other adrenergic drugs, corticoid hormones, thyroxin and other psychotropic drugs on the metabolism of adrenaline and other amines will be examined.

Part B included: Yes

Part B: Honors, Awards and Publications

Publications other than abstracts from this project:

Axelrod, J. and Tomchick, R. Activation and Inhibition of Adrenaline Metabolism. Nature, 184: 2022-2028, 1959.

Whitby, L.G., Hertting, G. and Axelrod, J. The effect of cocaine on the disposition of H^3 noradrenaline. Nature, 187: 4737, 1960.

Axelrod, J. Biochemical factors in the activation and inactivation of drugs. Naumyn-Schmiedeberg's Arch. exp. Path.u. Pharmak, 238: 24-34, 1960.

Axelrod, J. Amine metabolism and its pharmacological implications. Neuropharmacology. Trans. of the 5th Conference, The Josiah Macy, Jr. Found., 1960.

Invited to give lectures at:

University of Illinois Medical School
Merck, Sharp & Dohme
Maudsley Hospital, London

Serial No. M-CS-Ph-2
1. Laboratory of Clin.Science
2. Section on Pharmacology
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: The Physiological Disposition and Metabolic Fate of Drugs and Hormones Affecting the Nervous System.

Principal Investigator: Julius Axelrod

Other Investigators: Kopin,I., Whitby,L.G., Weil-Malherbe,H., Inscoe,J.K.

Cooperating Units: Psychopharmacology Research Center, NIMH

Man Years (calendar year 1960)	Patient Days (calendar year 1960)
Total: 2	None
Professional: 1 1/2	
Other: 1/2	

Project Description:

Objectives: This project is concerned with the absorption, excretion, plasma levels, rate of biotransformation, tissue distribution and metabolic pathways of drugs and hormones acting on the nervous system. Compounds under study are noradrenaline, normetanephrine, histamine, and melatonin.

Methods employed: Biochemical and pharmacological procedures.

Major Findings: Noradrenaline - Methods for the estimation of H^3-noradrenaline and H^3 normetanephrine have been developed. Noradrenaline is rapidly taken up in high concentration by the heart, spleen, and adrenal gland. These organs also retain the catechol amine for many hours. Within two minutes normetanephrine was found to be present in all tissues examined. Noradrenaline does not cross the blood-brain barrier except to a small extent in the hypothalamus. More noradrenaline appears to be bound to tissues than adrenaline.

In mice, 5 minutes after the intravenous injection of H^3 noradrenaline 50% of the H^3 catecholamine was metabolized. Most of the transformed hormone could be accounted for as normetanephrine.

After inhibiting catechol-O-methyl transferase with pyrogallol, a new metabolite 3,4-dihydroxyphenylglycol was found in the urine.

Melatonin: The tissue distribution and metabolism of this newly discovered hormone was studied. After the administration of melatonin it is rapidly metabolized to 6-hydroxy melatonin. The latter compound is then excreted as glucuronide and sulfate conjugates. All tissues including brain were able to take up melatonin.

Histamine: Methods for the estimation of C^{14} histamine and C^{14} methylhistamine have been developed. Preliminary work on the physiological disposition of these compounds have been carried out.

Significance to Mental Health Research: These studies should provide basic information concerning the physiological disposition of hormones and drugs affecting the nervous system.

Proposed course of project: The relative importance of O-methylation and deamination of the endogenous catecholamine hormones will be studied. The physiological disposition of C^{14} histamine, tyramine, amphetamine mescaline and other amines will be studied.

Part B included: Yes

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B: Honors, Awards and Publications.

Publications other than abstracts from this project:

Kopin, I.J., Pare,C.M.B., Axelrod,J., Weisbach,H. 6-Hydroxylation, the major metabolic pathway for melatonin. Biochim.Biophys.Acta, 40: 377-378, 1960.

Kopin,I.J. and Axelrod,J. 3,4-Dihydroxyphenylglycol, a metabolite of epinephrine. Arch.Biochem., 89: 148, 1960.

Axelrod,J., Weil-Malherbe,H., and Tomchick,R. The physiological disposition of H^3 epinephrine and its metabolite metanephrine. J.Pharmacol.and Expt. Therap. 127: 251-256, 1959.

Daly, J.W., Axelrod, J. and Witkop,B. Dynamic aspects of Enzymatic O-methylation and demethylation of catechols in vitro and in vivo. J.Biol.Chem., 235: 1155-1159, 1960.

Axelrod,J., Kopin,I.J. and Mann,J.D. 3-methoxy-4-hydroxyphenylglycol sulfate a new metabolite of epinephrine and norepinephrine. Biochim et Biophys.Acta., 36: 576-577, 1959.

Axelrod,J. Metabolism of epinephrine and other sympathomimetic amines. Physiol.Rev., 39: 751-776, 1959.

Axelrod,J. Dye methods for the estimation of basic drugs in Steward,C.J. and Stollman,A. Toxicology, Academic Press, p. 714-730, 1960.

Invited to participate in a Ciba Symposium on Adrenergic Mechanisms.

Invited to lecture at New York University Medical School.

Invited to present paper at the annual meeting of American College of Physicians.

Serial No. M-CS-Ph-3
1. Laboratory of Clin.Science
2. Section on Pharmacology
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A:

Project Title: Cellular Mechanisms in the Metabolism of Drugs and Hormones.

Principal Investigator: Julius Axelrod

Other Investigators: Weissbach,H., Albers,R.W. and MacLean, P.D., Daly,J.W. and Witkop, B.

Cooperating Units: NHI Laboratory of Clinical Biochemistry
NIMH Section on Limbic Integration
NINDB Laboratory of Neuroanatomical Sciences
NIAMD Laboratory of Chemistry

Man Years (calendar year 1960)	Patient Days (calendar year 1960)
Total: 1 1/2	None
Professional: 1	
Other: 1/2	

Project Description:

Objectives: This project is concerned with the enzymes involved in the formation and transformation of drugs and hormones. Under investigation are metabolic pathways of drugs and hormones catalyzed by enzymes, intracellular localization, biochemical mechanisms, specificity and species distribution of these enzymes.

Methods Employed: General biochemical and pharmacological procedures.

Major findings: The regional distribution of N and O methyl transferase in the nervous system was studied. Imidazole N-methyl transferase and cathechol -O- methyl were found to be present in all areas of the central nervous system. The highest concentration of the histamine methylating enzyme was found in the neurohypophysis while cathecol-O-methyl transferase was highly localized in the adenohypophysis. On the other

hand the melatonin forming enzyme was found only in the pineal gland.

The following enzymes for the formation and metabolism of melatonin have been found:

1. Serotonin + Acyl CoA $\rightarrow$ N-Acetyserotonin

2. N-Acetylserotonin + AMe $\rightarrow$ Melatonin

3. Melatonin $\xrightarrow{\text{TPNH O2}}$ 6-Hydroxymelatonin

Enzyme 1. was found to be present in most tissues and could acetylate many amines including histamine, tyramine tryptamine, and phenylethylamine.

Enzyme 2. was found only in the pineal gland and although it can O-methylate other indoles (serotonin, bufotenin) it is highly specific for N-acetylserotonin.

Enzyme 3. is present only in the liver and can 6-hydroxylate other indoles such as tryptamine, dimethyltryptamine and skatole.

Enzymes for the methylation of 3,4,5 trihydroxy phenylethylamine and demethylation of mescaline have been studied. Several new metabolites have been found.

Significance to Mental Health Research: These studies may make some contribution to the understanding of metabolic mechanisms in the nervous system in health and disease.

Proposed course of research: The enzyme involved in the conversion of noradrenaline to adrenaline will be investigated. Further studies on the amine acetylating enzyme will be made.

Part B included: Yes

Part B: Honors, Awards and Publications.

Publications other than abstracts from this project:

Axelrod, J. and Weissbach, H. Enzymatic-O-methylation of N-Acetylserotonin to melatonin. Science, 131: 1312, 1960.

Inscoe, J.K. and Axelrod, J. Some factors affecting glucuronide formation in vitro. J.Pharmacol.andExptl.Therap., 128: 128-131, 1960.

Axelrod, J. and Inscoe, J.K. Glucuronide formation of narcotic drugs in vitro and in vivo. Proc.Soc.Exp.Bio.Med., 103: 675-676, 1960.

Axelrod, J., Albers, R.W. and Clemente, C.D. Distribution of cathechol O-methyl transferase in the nervous system. Neurochem., 5: 68-72.

Senoh, S., Daly, J.W., Axelrod, J. and Witkop, B. Enzymatic p-O-methylation by catechol-O-methyl transferase. J.Am.Chem.Soc., 81: 6240-6245, 1959.

Brown, D.D., Tomchick, R. and Axelrod, J. The distribution and properties of a histamine metabolizing enzyme. J.Biol. Chem., 234: 2948-2950, 1959.

Weissbach, H., Redfield, B., Axelrod, J. Biosynthesis of melatonin: Enzyme conversion of serotonin to N-Acetylserotonin. Biochim.Biophys.Acta, 43: 362, 1960.

Conney, A.H., Gillette, J.R., Inscoe, J.K., Trams, E.R., Posner, H.S. Induced synthesis of liver microsomal enzymes which metabolize foreign compounds. Science, 130: 1478-1479, 1959.

Invited to participate in the 4th Internation Symposium on Neurochemistry, in Verenna, Italy, June 1960.

Serial No. M-P-A-1
1. Laboratory of Psychology
2. Section on Aging
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Age Differences in Learning and Transfer

Principal Investigator: Edward A. Jerome

Other Investigator: Eugene Streicher

Cooperating Units: None

Man Years:
Total: 2.20
Professional: .75
Other: 1.45

Patient Days: None

Project Description:

Objectives: The learning abilities of man and animals have been extensively studied, with great profit, in their developmental aspects, from the foetus to adulthood, and highly instructive correlations have been found between changes in the nervous system and changes in adaptive capacities over this portion of the life span. It is the purpose of the investigations planned under this project to extend studies of this nature through the years of maturity into senescence, a period in which adaptive changes hardly less dramatic than those of childhood are assumed to dominate the syndrome called "aging." Most of these changes are, of course, believed to be in the direction of impairment and the explanation that is most frequently adduced for this behavioral degeneration is the notion that it is a necessary concomitant of an ontogenetically determined deterioration of neural organization. It is the purpose of this project to secure, through the controlled observations of experiments, the information that is required to provide an adequate inferential basis for evaluating theories of aging, at least, insofar as they generate implications bearing on adaptive capacities.

Methods Employed: Because a very large proportion of the age-relevant physiological and biochemical work has been performed on the rat, this animal was chosen for the first series of studies under this project. A choice-escape apparatus, especially designed for the purpose, has

Part A.

Methods Employed (Continued:)

been employed in a set of experiments on behavioral stereotypy, learning, and transfer of training with contrasted age-groups. It was considered expedient to explore the potentialities of light-aversion as a source of activation in these experiments because the hunger drive is known to be age-related in such a manner as to completely confound motivational differences with anticipated age-differences in learning ability. Because the use of this drive in learning experiments is novel, it was considered desirable to undertake a parallel set of experiments designed to secure information on light-aversion as a source of motivation for aging animals. In this connection, two additional light-boxes have been designed to facilitate analysis of the regulation of behavior by control of illumination.

Major Findings: Observations on 100 animals have shown a marked tendency to stereotypy of free choice among five alternatives available in the escape apparatus. However, since there was no indication of age or sex differences in this connection, the test situation appears free of a possible source of group differences that would be artifactual relative to the purposes of the experiment. In a group of 80 animals working on a set of choice-problems representing a wide range of difficulties, senescent rats were found to learn as rapidly and efficiently as younger but mature animals. They also manifested as much positive transfer of training as the younger ones did.

Scientific Significance to the Program of Mental Health Research: Failure to detect an age-related learning deficit in rats, though supported by the early work of Stone, stands in need of corroboration within the species and extention to higher phyla, but, if the findings of these experiments can be corroborated and extended, they tend to confirm a currently growing conviction that learning deficits in aging humans may well be due, not to any universal biological predestination supported by inevitable tissue deterioration within the nervous system, but to the effects of attitudinal or behavioral patterns adopted by maturing individuals under the coercion of social conditions, customs and traditions that fail to provide the exercise necessary for the maintenance of the high level of learning skill achieved by the average young adult. Deterioration of this skill by disuse may be a great loss to the individual, to science and to society.

Proposed Course of the Project: During the coming year it is proposed to investigate possible age differences in (1) higher order response stereotypies, (2) the effects of certain drugs on light regulated behavior, (3) the effects of delayed reward in light regulated behavior.

Part B included No.

Serial No. M-P-A-3
1. Laboratory of Psychology
2. Section on Aging
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Age Changes in Mental and Perceptual Abilities and Personality Structure.

Principal Investigator: Jack Botwinick

Other Investigators: None

Cooperating Units: None

Man Years:
Total: 1.00
Professional: .50
Other: .50

Patient Days: 315
Inpatient Days: 205
Outpatient Days: 110

Project Description:

Objectives: In this project, normal age changes in mental and perceptual functions are investigated.

Methods Employed: Older and younger subjects are compared in speed of response in relation to variations in conditions of set and sense modality.

Scientific Significance to the Program of Mental Health Research: The most consistent finding in aging research is loss of speed with advanced age. Study of the conditions of set may help determine its role in the aging process as well as indicate methods of minimizing the effects of the loss.

Proposed Course of the Project: All (64) young subjects but only 15 elderly subjects have been tested. Emphasis will be directed toward obtaining data on 49 additional elderly subjects screened to be in good health. In addition, data will be analyzed and interpreted.

Part B included Yes.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B: Honors, Awards, and Publications

Publications other than abstracts from this project:

Botwinick, J., Brinley, J. F., and Robbin, J. S.: Maintaining set in relation to motivation and age. Amer. J. Psychol., 72: 585-588, 1959.

Botwinick, J., Robbin, J. S., and Brinley, J. F.: Age differences in card-sorting performance in relation to task difficulty, task set, and practice. J. Exp. Psychol., 59: 10-18, 1960.

Botwinick, J., and Kornetsky, C.: Age differences in the acquisition and extinction of the GSR. J. Geront., 15: 83-84, 1960.

Serial No. M-P-A-14
1. Laboratory of Psychology
2. Section on Aging
3. Bethesda

Incorporates Project Nos. M-P-A-6,7,9 & 10

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Effect of Age on the Blood-Brain Barrier, and Distribution of Substances Between Blood and Brain

Principal Investigator: Eugene Streicher

Other Investigators: None

Cooperating Units: None

Man Years:
Total: 2.15
Professional: .75
Other: 1.40

Patient Days: None

Project Description:

Objectives: The purpose of this investigation is to measure the rate of entry of ions, substrates, and drugs into the brain and their distributions at equilibrium.

Methods Employed: Materials are administered to rats by injection or by incorporation into experimental diets. The animals are eventually sacrificed and the blood and brain levels of the substances are measured.

Major Findings: To obtain a measure of the extracellular space of rat brain, the distribution of thiocyanate between blood and brain was ascertained. (Thiocyanate is considered to be impermeable to most cells). The "thiocyanate space" was found to be a function of dosage, and extrapolation of the curve relating extracellular volume to plasma level suggests a space of approximately 2-5 per cent. This figure is in general agreement with the estimates of electron microscopists, and indicates that, in contrast to liver or muscle, a large fraction of brain sodium and chloride is localized intracellularly. This conclusion was supported by measurements of brain extracellular space in rats in which cerebral edema had been experimentally induced. In this instance no change was observed in the distribution of thiocyanate,

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Individual Project Report
Calendar Year 1960

Part A.

Major Findings (Continued)

although the sodium content of the brain was elevated 50 per cent and that of the spinal cord was doubled.

The brain thiocyanate space of 2-1/2 year old rats was not significantly different from that of young animals indicating that possible brain changes in aging such as loss of cells, dehydration, gliosis, etc., if they do occur in rats, are not reflected in alterations of the extracellular space. On the other hand, in the case of heart, skeletal muscle, testes, and kidney, the extracellular compartment was significantly enlarged in the older animals.

Scientific Significance to the Program of Mental Health Research: The relatively small extracellular space of the brain suggests that the mechanisms governing the exchange of materials between blood and brain are somewhat different from those of other tissues. Diffusion distances between cells and between cells and capillary bed are apparently small. Possibly the small extracellular space rather than the blood-brain barrier may be responsible for the apparent exclusion of certain compounds from the brain.

Proposed Course of Project: Terminate

Part B included Yes.

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Individual Project Report
Calendar Year 1960

Part B: Honors, Awards, and Publications

Publications other than abstracts from this project:

Streicher, E.: Measurement of the extracellular space of brain. An invited paper to be published in a commemorative volume in honor of Dr. Harold E. Himwich on the occasion of his 65th birthday. In Press

Streicher, E.: The thiocyanate space of rat brain. In Press

Streicher, E.: The thiocyanate space of rat brain in experimental cerebral edema. In Press

Serial No. M-P-A-15
1. Laboratory of Psychology
2. Section on Aging
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: An Analysis of Age Differences in Speed, Accuracy, and Association Habits in Mental and Psychomotor Tasks.

Principal Investigator: James E. Birren

Other Investigators: None

Cooperating Units: None

Man Years:
Total: 2.33-1/3
Professional: .33-1/3
Other: 2.00

Patient Days: 184
Inpatient Days: 92
Outpatient Days: 92

Project Description:

Objective: The purpose of this project is to explore the nature of possible age differences in psychological processes such as concept formation and verbal associations, in relation to more elementary functions such as response speed and association speed and to association strengths. The general objective is to determine to what extent the major age differences in performance characteristics are the result of habit, as in language usage, or in endogenous changes in the functions of the central nervous system.

Methods Employed: Old and young human subjects will be systematically observed in a series of tasks from simple, and choice reaction time to speed of verbal associations. Insofar as possible all stimuli will be presented in a standard apparatus, the Psychomet, which permits measurements of individual response times.

Scientific Significance to the Program of Mental Health Research: It is of considerable significance to know whether the psychological characteristics of older persons are relatively more influenced by custom and associations or whether endogenous factors such as speed of central nervous system functioning are dominant. If the major determinants of the age differences in behavior are identified, it may be possible to manipulate the variables in future experiments. The ultimate concern is with maintaining maximum adaptive capacity by rational control of restrictive factors.

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Individual Project Report
Calendar Year 1960

Part A.

Project Description (Continued):

Major Findings: A set of 22 problems, programmed by the Psychomet and differing widely with respect to their demands on associative proficiency, have been administered to two contrasting age-groups of human subjects. The results available at present indicate that the relative speed-impairment associated with aging increases as the complexity of the mental functions required by a problem increases. The apparent age-decrement in speed of performance on tasks requiring such mental operations as color-symbol matching, superordinate, coordinate and part-word association far exceeded that which could be explained in terms of purely motor deficits measured in analogous situations that did not require exercise of the cognitive functions in question.

Proposed Course of the Project: During the current year, data will be secured from additional subjects and the full set of results will be submitted to an analysis designed to partition variances among the several associative processes that are found to deteriorate with age.

Part B included Yes

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B: Honors, Awards, and Publications

Publications other than abstracts from this project:

Birren, J. E., Riegel, K. F., and Morrison, D. F.: Intellectual capacities, aging, and the nature of man's environment: A discussion of issues and a report of experimental findings. In Press

Birren, J. E., and Riegel, K. F. Age differences in response speed as a function of controlled variations of stimulus conditions: lights, numbers, letters, colors, syllables, words, and word relationships. In Press

Serial No. M-P-A-16
1. Laboratory of Psychology
2. Section on Aging
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: A Study of the Higher Cognitive Processes in Aging Human Subjects.

Principal Investigator: Edward A. Jerome

Other Investigators: None

Cooperating Units: None

Man Years:
Total: 1.00
Professional: .50
Other: .50

Patient Days: 220
Inpatient days: 60
Outpatient days: 160

Project Description:

Objectives: It is the purpose of this project to identify, analyze and evaluate the deficits of the aging individual in an area of behavior that requires the exercise of "complex mental processes." Processes of this kind are usually accepted as including such comprehensive activities as thinking, logical reasoning, hypothesis formation and problem-solving, all of which are of paramount importance for normal and successful operation in society.

Methods Employed: The Psychological Corporation's Logical Analysis Device (LAD) is being employed to program a set of exploratory problems while we are designing our own apparatus which will control a large variety of problems especially adapted to the capacities and interests of the aging individual as they are identified in this exploratory work. Some additional problems, e.g., the games of Nim and Peggety, have been used with a selected few of the old subjects.

Major Findings: In a group of 20 young and 11 old subjects who were given a complete course of testing with the Logical Analysis Device the following specific deficits were prominent in the performances of the aged: (1) failure to secure clear identification of sub-goals before engaging in trials-and-error search, (2) failure to take advantage of mnemonic aids urged upon them by the procedure, (3) inability to develop solution strategies designed to reduce the cognitive strain

Serial No. M-P-A-16
1. Laboratory of Psychology
2. Section on Aging
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Major Findings (Continued)

of the problem-solving effort, (4) inability to apply strategies that were repeatedly explained, (5) failure to draw inferences appropriate to the information at hand. The conclusion suggested by these results is that during later life there is a general deterioration of the fundamental heuristic principles acquired during later youth or early maturity.

Scientific Significance to the Program of Mental Health Research: The investigations planned under this project may be expected to contribute importantly to a completion of the developmental schema by extending the work of the child psychologist through the periods of adulthood and senescence. Knowledge of changes in the heuristic proficiency of the aging individual is, of course, necessary for any adequate appraisal of his adaptive status. According to all current psychological interpretations, the heuristic processes impugned by these tests are of basic importance to adaptive behavior in real life situations. It is anticipated that this project will provide a sufficiently detailed profile of the aging person's heuristic deficits to permit the planning of an inquiry into methods of re-education designed to maintain his adaptive capabilities.

Proposed Course of the Project: In order to secure an adequate inferential basis, it will, of course, be necessary to employ a variety of problems selected to provide for representation of most of the factors believed to be necessary for successful and efficient problem solving. During the present year, performance on two additional problems will be studied as soon as programming devices that are currently under construction have been completed. It is also planned to test some schizophrenic patients in order to compare their performances with those of aging persons.

Part B included No.

Serial No. M-P-A-17
1. Laboratory of Psychology
2. Section on Aging
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Animal Learning

Principal Investigator: Jack Botwinick

Other Investigators: None

Man Year:
Total: 1.95
Professional: .50
Other: 1.45

Patient Days: None

Project Description:

Objective: The object of this study is to answer the question whether advanced age of an infra-human species is associated with difficulty in modifying habits. As indicated last year, an auxillary objective includes the determination of possible age changes in hunger motivation, and food intake as it is related to learning.

Methods Employed: Three age groups of Sprague-Dawley rats, approximately 4, 9, and 22 months, are compared in learning a position response in a T-maze, and in ability to reverse from this position to the alternate one. In addition, rats are tested for continuous relearning of alternate positions.

Food intake, weight and running measures are also made on selected animals.

Scientific Significance to the Program of Mental Health Research: A finding of deficit with age in modifying response would demonstrate the biological generality (i.e., the similarity among phyla) of the problem. In addition the role of motivation in aging processes would contribute to general field of learning.

Proposed Course of Project: Studies will be enlarged to include more difficult tasks, variations of the mode of response, and replication of results.

Part B included No

Serial No. M-P-A-18
1. Laboratory of Psychology
2. Section on Aging
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Age Differences in Perceptual Processes

Principal Investigator: Richard M. Warren

Other Investigators: None

Cooperating Units: None

Man Years:
Total: 1.20
Professional: 1.00
Other: .20

Patient Days: 75
Inpatient Days: 25
Outpatient Days: 50

Project Description:

Objectives: To compare perceptual processes in young and old humans.

Methods Employed: A loop of recording tape containing a single statement of a word or phrase was used as a source of repetitive verbal stimulation. Listening to such repetitive stimulation results in illusory perceptual changes, frequently involving considerable phonetic distortion.

Major Findings: Illusory auditory transitions of repeated words occur about four times more rapidly with young than with aged subjects. In addition, the responses of older people are affected by the frequency of occurrence of words in English usage to a much greater extent than for younger people. There is evidence for greater emphasis of organization on a phonemic rather than verbal level in the young.

Scientific Significance to the Program of Mental Health Research: It appears that the manner in which stimuli are organized perceptually changes with age. The greater perceptual stability and reliance upon probability of occurrence suggest that older people may perform better than younger individuals at certain tasks.

Proposed Course of Project: Further analyses of the data on age differences in auditory perception of repeating words is in progress.

1. Laboratory of Psychology
2. Section on Aging
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Purposed Course of Project: (Continued)

Visual perception will be studied to see if analogous age differences exist. Other related age differences in perception will be studied.

Part B included Yes

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B: Honors, Awards, and Publications

Publications other than abstracts from this project:

Warren, R. M., Poulton, E. C.: Basis for lightness-judgments of grays. Amer. J. Psychol., 23: 380-387, 1960.

Warren, R. M.: An auditory analogue of the visual reversible figure. Amer. Psychologist, 15: 499, 1960.

Serial No. M-P-A-19
1. Laboratory of Psychology
2. Section on Aging
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Age-Differences in the Effects of Stress in the Albino Rat.

Principal Investigator: James E. Birren

Other Investigators: None

Cooperating Units: None

Man Years:
Total .78-1/3
Professional: .33-1/3
Other: .25

Patient Days: None

Project Description:

Objective: It is the purpose of this project to explore the nature of possible age-differences in the ability to sustain continuous psychomotor performance and the possible relation of such differences to learning ability.

Methods Employed: Contrasting age groups of rats will be tested in a variety of tasks in which the swimming escape effort will be employed as the motivating condition.

Scientific Significance to the Program of Mental Health Research: Age related decrements in the speed of simple response to unitary stimuli have been studied in detail, but there is a serious need for data on the relation of speed to age in performances that require a sustained sequence of responses organized under a specific goal oriented set. This type of information is essential to the development of any theory of aging that is intended to generate implications relevant to the complex behavioral patterns characteristic of normal interaction with a natural environment.

Major Findings: In a preliminary study of swimming proficiency and fatigability using a straightway course, statistically significant age-differences in speed were found in both male and female rats. Old males, however, not only fatigued more rapidly than other sex-age

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Major Findings: (Continued)

groups but also recovered more slowly than the others did. In another study with the same apparatus it was found that while extended swimming practice improved resistance to fatigue in all sex-age groups, old males, originally the least resistant, improved the most. On the other hand, there was no indication that extended practice increased the maximum swimming speed, i.e., the speed prior to fatigue. An attempt to decrease the rate of fatigue by the use of eserine and benzedrine was not successful because the swimming performance became disorganized as a side effect of the drugs at the doses employed.

The initial part of a learning experiment using a two choice-point water-maze has been completed. Preliminary analysis of the data did not reveal an age-difference in the rate of learning.

Proposed Course of the Project: When the animals trained in the water-maze have been withheld from practice for several months, a relearning test on the same pattern will be given. When they have achieved the criterion of mastery on this task, they will be given a new maze pattern to learn.

Part B included No.

Serial No. M-P-B-2
1. Laboratory of Psychology
2. Section on Animal Behavior
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: The analysis of the relationships between problem-solving behavior as demonstrated in the delayed-response, discrimination, and learning-set tasks and certain cortical and subcortical structures in the subhuman primate brain.

Principal Investigator: H. Enger Rosvold

Other Investigators: Drs. Stefan Brutkowski (Visiting Scientist until July), Charles Butter (NIMH Fellow)

Cooperating Units: None

Man Years:
Total: 2-1/2
Professional: 1
Other: 1-1/2
(In addition, Dr. Stefan Brutkowski, Visiting Scientist and Dr. Charles M. Butter, NIMH Fellow)

Patient Days:
Total: None

Project Description:

Project: To identify the brain structures that are essential for delayed-response types of behavior and to describe the changes in this behavior which follow lesions in these structures.

Objectives: To determine the cerebral organization subserving problem-solving behavior and to describe the nature of the behavioral dysfunction which follows damage to the brain structures comprising this organization.

Methods Employed: (1) Chimpanzees. Chimpanzees are trained on a variety of delayed-response, discrimination, and learning-set tasks, subjected to prefrontal lesions and retested.

(2) Monkeys. (a) Lesions are placed in those subcortical structures which have been shown to be important for delayed-response functions. The animal's performance on visual discrimination and delayed-response type tests is compared with that of monkeys and chimpanzees which have lesions in the prefrontal lobes.

(b) Lesions are placed in dorsolateral frontal cortex and the animals tested on a variety of tests which demand frequent switching of responses. Lesions are placed in orbital frontal cortex and the animals tested on a variety

Part A.

Methods Employed (Continued)

of tests which demand inhibition of responses. The effects of these two lesions are contrasted in an attempt to specify the degree to which "loss of inhibition" and "perseveration" is involved in the delayed-response deficit which follows damage to the prefrontal lobes.

(c) The performance of animals with lesions in dorsolateral frontal cortex and in auditory cortex are compared on auditory tests. The study is designed to contrast the causes for the apparently similar deficit following these two lesions: in animals with frontal lesions the impairment on discrimination problems is due to non-sensory factors, while in animals with auditory cortex lesions it is due to sensory factors.

(d) Unilateral lesions are placed in the prefrontal lobes of monkeys and of chimpanzees. The animals are then tested for learning and for retention of delayed alternation and delayed response.

Major Findings: (1) Chimpanzees. It has been confirmed in four additional subjects that the chimpanzee, unlike the monkey, recovers almost completely from an initial deficit on delayed-response problems. In addition, it has been possible to show in four chimpanzees that if the delayed-response problem is made more difficult, the chimpanzee has a severe and permanent deficit. This would indicate that the chimpanzee with a frontal lesion is quantitatively, rather than qualitatively, superior to the monkey with a frontal lesion. Quantitative differences have also been shown for animals with unilateral lesions.

(2) Monkeys. (a) An earlier study implicated posterior mid-line structures near the splenium of the corpus callosum in delayed-alternation performance; it was not possible to decide, however, which of several structures was critical for the effect. In 22 animals, lesions have been placed in the splenium itself, in the hippocampal commissure, habenula, dorso-medial nucleus of the thalamus, stria medullaris, body of the fornix, or in the posterior columns of the fornix. Only in animals in which the lesion involves the latter structure is there impairment in delayed alternation performance.

(b) In four separate studies, involving a total of 32 animals, the degree to which "loss of inhibition" and "perseveration" are related to delayed response deficits has been investigated. The first of these has compared normal, frontal and temporal animals on a series of tests designed to require the animal to switch responses frequently in order to be correct. This study has shown in learning-set, discrimination reversal, and one-trial learning problems that frontal animals have abnormally strong perseverative tendencies which preclude success. In the second set of experiments, animals with dorso-lateral frontal lesions have been compared with animals with orbital frontal lesions on a series of discrimination and problem-solving tasks. This study has shown that when the problem requires the animal to withold a response in

Part A.

Major Findings (Continued)

order to be correct, the animal with the orbital lesion is inferior to that with the dorsolateral. In the third set of experiments, the extinction of a food-rewarded instrumental response is being studied in monkeys with lateral frontal and orbital lesions. In general the results of this study indicate that animals with frontal lesions show extinction rates comparable to those in normal animals, but animals with orbital lesions extinguish more slowly. These findings, as in the second experiment, suggest that orbital animals have considerably more difficulty than other animals in withholding or inhibiting responses. The fourth study is designed to test the hypothesis that motivational changes account for the loss of inhibition in orbital monkeys. Initial results are in the direction of confirming the hypothesis. Taken together these studies provide a consistent account of frontal-lobe function which is more comprehensive than earlier theories and is more consistent with the large body of evidence pertaining to the effects of frontal injury in man.

(c) Eight monkeys have been involved in this study which is designed to contrast the non-sensory function of the frontal association cortex with the sensory function of posterior association cortex. Only preliminary data are so far available, but early results indicate that the impaired performance of the animals with auditory cortex lesions on discrimination tasks is due to their inability to distinguish the auditory stimuli; by contrast the impaired performance on these tasks of the animals with frontal lesions is due to an inability to withhold responses to the negative stimuli.

Scientific Significance to Mental Health Research: The results of this project, which show that the effects of frontal lobe lesions in chimpanzee and monkey differ mainly in quantitative respects, suggest not only that the results of studies in monkeys and chimpanzees may be extended to man, but also that methods similar to delayed-response type performance may be used with man as well. More specifically the results suggest that other areas, even other association areas, do not assume the functions of frontal cortex when it is injured, nor does one frontal area serve adequately the function of both. Furthermore, the results suggest that the frontal lobes are predominantly involved in integrating information from several sensory modalities and in transforming this information into responses adequate to the demands of a situation. Switching of responses in adjusting to changes in situation appears to be a primary function of the frontal lobes; disease or injury appears to result in an inability to make these rapid adjustments.

Proposed Course of the Project: This project will continue very much in the same direction. Chimpanzees will be used to explore the effects of frontal lesions on more complex variations of the delayed-response task. In monkeys, the analysis will proceed along two main directions: (a) to determine what other structures than frontal cortex and caudate nucleus are involved in delayed-response performance (b) to provide a more precise description of the "perseverative" tendencies which follow

Part A.

Proposed Course of the Project (Continued)

frontal-lobe loss in an attempt to develop a more comprehensive conception of frontal lobe functions.

Part B included Yes X No ___

Part B. Honors, Awards, and Publications

Publications other than abstracts from this project:

Battig, K., and Rosvold, H. E.: Die Wirkung von Nucleus caudates und Frontal hirnschaden auf aufgeschobene Reaktionen beim Macacus-Rhesus-Affen. Helv. Physiol. Acta. 17: 12-13, 1959.

Battig, K., Rosvold, H. E., and Mishkin, M.: Comparison of the effects of frontal and caudate lesions on delayed response and alternation in monkeys. J. Comp. Physiol. Psychol. 53: 400-404, 1960.

Battig, K., and Rosvold, H. E.: Das visuelle und akustiche Lernvermorgen von frontalherngeschadigten Macacus-Rhesus-Affen. Helv. Physiol. Acta. 18: 7-9, 1960.

Brush, Elinor, Mishkin, M., and Rosvold, H. E.: Effects of object performances and aversions on discrimination learning in monkeys with frontal lesions. J. Comp. Physiol. Psychol. 54: 1961 (In press).

Rosvold, H. E., Szwarcbart, Maria, Mirsky, A. F., and Mishkin, M.: The effect of frontal lobe damage on delayed response performance in chimpanzees. J. Comp. Physiol. Psychol. 54: 1961 (In press).

Rosvold, H. E., and Mishkin, M.: Non-sensory effects of frontal lesions on discrimination learning and performance. In Delafresnaye, J. F. (ed.): Brain Mechanisms in Learning. Oxford, Blackwell, 1961 (In press).

Rosvold, H. E.: Electroconvulsive shock. In Encyclopedia of Science and Technology. New York, McGraw-Hill Book Company, 1960 (In press).

Rosvold, H. E.: Memory. In Encyclopedia of Science and Technology. New York, McGraw-Hill Book Company, 1960, pp. 216-222.

Serial No. M-P-B-4
1. Laboratory of Psychology
2. Section on Animal Behavior
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Analysis and comparison of the effects of drugs and brain pathology on measures of attentive behavior.

Principal Investigator: Allan F. Mirsky

Other Investigators: Dr. Ann Lodge (NIMH Fellow)

Cooperating Units: Neurosurgical Branch, NINDB, Clinical Science, NIMH

Man Years:
Total: 1-1/2
Professional: 1/2
Other: 1
(In addition, Dr. Ann Lodge, NIMH Fellow since October)

Patient Days:
Total: 25

Project Description:

Project: Analysis and comparison of the effects of drugs and brain pathology on measures of attentive behavior.

Objectives: The objectives of this project include two related areas of investigation: (1) To assess the effects of various types of brain pathology on measures of attentive behavior, such as provided by the Continuous Performance Test (C.P.T.). (2) To investigate the effects of drugs on these same measures, so as to gain information relative to the functions and brain loci tapped by these tests.

Methods Employed: Individuals with brain pathology and normal and pathological controls are tested under various conditions, including drugs, on measures of attentive and intellectual behavior.

Major Findings: During the past year, the major effort in the study of attentive behavior has been devoted to the analysis of the relationship between test performance and E.E.G. and other physiological variables. This work is described more fully in project No. M-P-B-8. A study has been undertaken, however, as the Ph.D. dissertation of a student at Catholic University (Mr. Eugene Stammeyer) in which the dissociation between the effects of various agents on different psychological tests serves as the dependent variable in an investigation of differences among various psychopathological groups. The dissociation, briefly described, is between the effects of agents which presumably exert their major effect on the cerebral

Part A.

Major Findings (Continued)

cortex (e.g., low doses of barbiturate drugs) and those which act on deeper structures in the area of the reticular activating system (chlorpromazine, sleep deprivation). The latter agents produce more impairment in the performance of the Continuous Performance Test (C.P.T.) than in that of the Digit Symbol Substitution Test (D.S.S.T.). The reverse effect is produced by the barbiturates. If it is true that schizophrenia may be conceived as a disturbance in an individual's capacity to attend to, monitor, or gate incoming stimuli and if it is true that these functions are mediated largely via the reticular activating system then it might be expected that the previously described dissociation would differ in schizophrenic and normal individuals. That is to say, relatively more or longer-lasting disruption would be expected in a schizophrenic group (as the result of their defective gating processes) on tests dependent upon subcortical functioning than on tests measuring other functions. A study was designed in which normal, schizophrenic and hospitalized neurotic subjects were administered either the C.P.T. or the D.S.S.T. before, during and after the effects of various distracting stimuli. Preliminary results indicate that the schizophrenic subjects are more impaired than either of the other two groups by the distracting stimuli. The impairment is evident in both the D.S.S.T. and the C.P.T.; however, performance on the latter test appears to be more impaired and to take longer to recover than on the D.S.S.T. These results seem to afford some preliminary support for the notion of disordered subcortical functioning in schizophrenia and for the utility of this type of approach in studying psychopathological disturbances.

Scientific Significance to Mental Health Research: This research contrasting the effects of different kinds of agents upon different tests leads to a better understanding both of the functions measured by the tests and of the locus of effect of the centrally-acting agents themselves. Application of this type of technique to other centrally-acting drugs may prove helpful in understanding their effects on behavior. In addition, application of the technique to various psychopathological groups may help to elucidate the role of brain structures in relation to disordered behavior. The precise way in which the brain is involved in such disease entities as schizophrenia, for example, is largely unknown.

Proposed Course of Project: The most compelling need in the area of psychopharmacology is to understand the basis of the effect of the psychoactive drugs on disordered behavior. Thus, the most fruitful direction which this kind of research effort could take would involve application of the techniques devised in the study of normal controls to the study of psychotic groups. Several studies indicate that such groups respond differently from normal individuals to the effects of psychoactive agents. Further work of this sort, in which the drug response profiles of various tests are studied in psychotic patients, may provide useful leads to an under-

Part A.

Proposed Course of Project (Continued)

standing of how the psychoactive drugs exert their salutary effects on behavior and may aid in identifying brain structures that are involved in the development or manifestation of the psychotic condition. Studies planned for the coming year include investigation and comparison of the effects of low and high doses of barbiturates on the C.P.T. and the D.S.S.T.; high doses of the drug should resemble the behavioral effects of chlorpromazine and sleep deprivation more than those of low doses of barbiturates. Other studies will be directed towards exploring and refining further the functional differences between the D.S.S.T. and the C.P.T.

Part B included Yes X No ____

Part B. Honors, Awards, and Publications

Publications other than abstracts from this project:

Mirsky, A. F., and Rosvold, H. E.: The use of psychoactive drugs as a neuro-psychological tool in studies of attentive behavior in man. In Miller, J. G., and Uhr, L. (eds.): Drugs and Behavior. New York, Wiley, 1961, (In press).

Mirsky, A. F., Primac, D. W., Ajmone-Marsan, C., Rosvold, H. E., and Stevens, J.: A comparison of the psychological test performance of patients with focal and nonfocal epilepsy. Exper. Neurol. 2: 175-189, 1960.

Mirsky, A. F.: Gibbs, F. A. (ed): Molecules and Mental Health. Book review in J. Nerv. Ment. Dis. 130: 1960, 86-88.

Townsend, A., and Mirsky, A. F.: A comparison of the effects of meprobamate, phenobarbital and d-amphetamine on two psychological tests. J. Nerv. Ment. Dis. 130: 212-216, 1960.

Under terminated project M-P-B-3 (1959) the following publications appeared:

Mirsky, A. F.: Studies of the effects on brain lesions on social behavior in Macaca mulatta: methodological and theoretical considerations. Ann. N. Y. Acad. Sci. 85: 785-794, 1960.

Serial No. M-P-B-5
1. Laboratory of Psychology
2. Section on Animal Behavior
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Defining the role in vision of an extrageniculostriate visual system.

Principal Investigator: Mortimer Mishkin

Other Investigators: Charles M. Butter (NIMH Postdoctoral Fellow) and Mr. Thomas Brown (NIMH Predoctoral Fellow)

Cooperating Units: None

Man Years:
Total: 1-1/2
Professional: 1/2
Other: 1
(In addition Dr. Charles M. Butter, NIMH Postdoctoral Fellow and Mr. Thomas Brown, Predoctoral Fellow)

Patient Days:
Total: None

Project Description:

Project: Analysis of the behavioral effects of inferotemporal lesions in monkeys.

Objectives: The finding of severe visual impairment in monkeys with inferotemporal lesions raised the question as to whether or not there was any anatomical relationship between the inferotemporal region and the striate cortex. On the basis of recently completed experiments the conclusion has now been reached that the two areas are indeed closely related, and that the connections between them are mainly, if not exclusively, cortico-cortical. Follow-up experiments are being carried out to provide additional information about these connections, but in general, now that a satisfactory rationale has been provided for the involvement of inferotemporal cortex in vision, the emphasis of the project is gradually being shifted toward a more precise behavioral analysis of the visual impairment.

Methods Employed: (1) Having demonstrated that the inferotemporal and striate areas are connected by indirect cortico-cortical pathways, work in the past year has attempted to locate the intermediate cortical areas through which the pathway is relayed. The method involves preparing animals with unilateral striate and contralateral inferotemporal lesions, and then attempting to interfere with visual discrimination performance by destroying the intermediate cortical area through which the one remaining connection

Part A.

Methods Employed (Continued)

passes in crossing from the intact striate area in one hemisphere to the intact inferotemporal area in the opposite hemisphere. (2) It was previously demonstrated that the crossed connection described above may be destroyed by cutting the posterior third of the corpus callosum. To determine whether or not the discrimination impairment thus produced is simply a by-product of visual field defects, animals with the appropriate lesions are tested on a discrimination task presented in their intact field of vision only (i.e., the field contralateral to their intact striate area). (3) It is now established that the visual deficit produced by cutting striate-temporal connections or by ablating the inferotemporal cortex bilaterally involves discrimination learning more than it does visual acuity or visual thresholds. But the nature of the visual learning involved still eludes precise definition. Experiments are underway which attempt to distinguish between two possible types of visual learning impairment - perceptual vs. associative losses. In one experiment, which employs a filmed sequence of pairs of stimuli, animals are trained to press a lever whenever the two stimuli in the pair are identical, and to refrain from responding when the two stimuli are dissimilar. After learning this film they are transferred to a second film employing new visual stimuli. Failure to transfer correctly would provide support for the view that the impairment is due to a perceptual loss. (4) A second experiment aimed at the same problem employs stimulus generalization techniques. Since these minimize associative learning, any impairment in the generalization of inferotemporal animals might again be attributable to perceptual loss. (5) While the research outlined above has provided a sound rationale for ascribing visual functions to the inferotemporal cortex, other studies have reopened the issue as to whether the functions of inferotemporal cortex are exclusively visual or whether they embrace olfactory functions as well. Studies have been undertaken aimed at precise localization of a temporal-lobe region serving associative functions in olfaction.

Major Findings: (1) Preliminary results implicate prestriate and parietal areas as intermediate relay stations along the striate-inferotemporal pathway. (2) The impairment produced by destroying the striate-inferotemporal pathway appears not to be a by-product of visual field defects, but one that is qualitatively similar to the learning impairment produced by bilateral inferotemporal lesions. (3) Preliminary results favor an interpretation in terms of a perceptual learning loss as opposed to an associative learning loss. (4) The range of stimulus generalization has been determined for normal animals; operated animals are currently being trained. (5) The results of the first study on the localization of an olfactory area suggest that such a focus may lie in the polar region of the temporal lobe. A second study to test this possibility more directly is well underway.

Scientific Significance to Mental Health Research: Vision is perhaps the best understood of the sensory modalities in relation to the functioning of the nervous system. Yet a major

Part A.

Scientific Significance to Mental Health Research (Continued)

problem remains unsolved in vision as it does in all sensory modalities: Delineation of the events which intervene between stimulus reception at the cortex and the observed response. The demonstration that damage to the inferior convexity of the temporal lobes in monkeys produces impairment in visually-guided behavior has opened up the hitherto inaccessible area of the intracerebral processes in vision, i.e., neural activity related to vision but beyond the level of the striate cortex. Unravelling these mechanisms in vision should aid greatly in the solution of a general problem for psychology, viz., accounting for the intervening neural processes (thought and its breakdown) in normal and abnormal behavior.

Proposed Course of Project: All of the experiments outlined above will be continued to completion.

Part B included Yes X No ____

Part B. Honors, Awards, and Publications

Publications other than abstracts from this project:

Butter, Charles, M., and Campbell, Byron A.: Running speed as a function of successive reversals in hunger drive level. J. Comp. Physiol. Psychol. 53: 52-54, 1960. (Work done at Harvard)

Mishkin, M., and Weiskrants, L.: Effects of cortical lesions in monkeys on critical flicker frequency. J. Comp. Physiol. Psychol. 52: 660-666, 1959.

Serial No. M-P-B-6
1. Laboratory of Psychology
2. Section on Animal Behavior
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: A comparative study in primates on the effects of temporal lobe damage on visually guided behavior.

Principal Investigator: Mortimer Mishkin

Other Investigators: None

Cooperating Units: Section on Clinical Psychology, Surgical Neurology Branch, NINDB, Laboratory of Clinical and Social Psychology, Forest Glen Section, Walter Reed Army Institute of Research.

Man Years:
Total: 1
Professional: 1/2
Other: 1/2

Patient Days:
Total: 50

Project Description:

Project: Effects of temporal lobe damage on visually guided behavior in monkeys, chimpanzees, and man.

Objectives: Damage to the neocortex of the temporal lobes produces impairment in visually-guided behavior both in monkeys and baboons. This project attempts to determine whether similar impairment may be produced by temporal-lobe damage in the chimpanzee and in man.

Methods Employed: (1) Chimpanzees are trained on a variety of visual tasks (similar to those used with monkeys and baboons) before operation, after unilateral temporal neocortical damage, and after bilateral damage. Unoperated chimpanzees as well as chimpanzees with different cerebral lesions serve as controls. (2) Human subjects with focal temporal-lobe epilepsy are tested on a variety of visual discrimination tasks before and/or after unilateral temporal-lobe surgery for relief of epilepsy. The tests include (a) a difficult visual learning task analogous to the simpler tasks used with animals, (b) The McGill Picture Anomalies test, and (c) a tachistoscopic test comparing recognition in the left and right visual fields.

Major Findings: (1) While chimpanzees are unaffected by unilateral inferotemporal damage, they have shown visual impairment following bilateral damage. Similar impairment has not been found in a control group

Part A.

Major Findings (Continued)

with frontal-lobe damage. However, contrary to results with lower primates similar impairment has been found in a control group with lesions intended for the temporal pole and amygdala. The answer to whether this finding represents a true phylogenetic difference in functional localization between monkeys and chimpanzees, or is due instead to unintended overlapping temporal-lobe damage in the two chimpanzee groups, must await histological verification of the lesions. (2) On the basis of data accumulated over the past three years, it appears that patients with unilateral temporal-lobe epilepsy and/or surgery are indeed impaired on visual discrimination tests (a) and (b) described above. However, this finding is a curious one for two reasons. First, confirming reports by Milner at the Montreal Nuerological Institute, the impairment seems to be restricted to patients with temporal-lobe pathology in the right hemisphere. Secondly, as indicated above, neither monkeys nor chimpanzees exhibit any visual impairment following only unilateral temporal-lobe damage. Considered together these facts point toward a greater specialization of function within the association cortex of man than within that of lower primates.

Before the positive results just described had been accumulated, it was hypothesized that unilateral injury might produce demonstrable visual impairment if vision were confined to the field opposite the injury. Task (c) was designed to test this hypothesis, and the results have confirmed the prediction. Thus, patients with left temporal lobectomy show a loss of recognition in the right visual field as compared with the left, while the reverse is true for patients with right temporal lobectomy. These results do not appear to be due to direct involvement of the primary visual system. Here, then, with a more sensitive indicator, a visual impairment has been revealed in man after temporal-lobe damage in either hemisphere.

Scientific Significance to Mental Health Research: The assumption underlying neuropsychological experiments conducted on animals, particularly rhesus monkeys, is that any brain-behavior relationship there discovered will contribute to an understanding of normal and pathological brain function in man. This assumption has been amply supported by comparative data on the functions of sensory and motor cortex. Now, reliable data are becoming available concerning the functions served in monkeys by "association cortex". This project attempts to apply these recent findings to aid the study of the functions of "association-cortex" in man. The chimpanzee, which may be considered to lie intermediate to man and monkey, both from an anatomical and a behavioral standpoint, serves as an experimental bridge in this comparative study.

Proposed Course of Project: The experimental work has been completed, the data are now undergoing final analysis and the various studies are being prepared for publication.

Part B included Yes ___ No X

Serial No. M-P-B-7
1. Laboratory of Psychology
2. Section on Animal Behavior
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Histological Analysis of Cerebral Lesions and Intracerebral Connections in Primates.

Principal Investigator: Maria K. Szwarcbart

Other Investigators: Dr. H. G. Kuypers (Consultant)

Cooperating Units: None

Man Years:
Total: 2
Professional: 1
Other: 1

Patient Days:
Total: None

Project Description:

Project: Verification of lesions and electrode placements in chronic experimental animals, and analysis of intracerebral connections in acute preparations.

Objectives: The objective of the first part of this project is to delineate the loci of the lesions and electrodes which produce specific behavioral effects, and of the second, to determine whether or not loci yielding similar effects are anatomically interconnected.

Methods: When the behavioral testing of chronic experimental animals is completed, their brains are embedded in either celloidin (large specimens) or paraffin (smaller specimens), sectioned, stained for cells and fibers, examined microscopically, and electrode tracks and lesions reconstructed. In the second part of the project, animals are prepared with selective lesions purely for anatomical investigation. The animals are sacrificed within a few days after surgery and their brains prepared in frozen sections, stained for degenerated fibers, and examined microscopically to determine the locus, extent and course of degenerating fibers.

Major Findings: In the first part of this project, electrode tracks in four monkeys and brain lesions in two chimpanzees, 55 monkeys, and two dogs have been analyzed in the past year. All of these animals had served as subjects in psychological studies. The earlier findings have been confirmed: lesions restricted to inferotemporal neocortex produce visual

Part A.

Major Findings (Continued)

discrimination deficits; lesions restricted to striate cortex produce visual acuity impairment; lesions restricted to frontal cortex or to the head of the caudate nucleus produce delayed-response deficits. A series of selective ablations in the area of the splenium of the corpus callosum has revealed that the posterior columns of the fornix may also be involved in delayed response tasks. In addition, histological verification of the extent and locus of seriatim lesions in the same animal in inferotemporal cortex, striate cortex, and corpus callosum has contributed to the delineation of an extrageniculate system for visual discrimination. Also, verification of the site of implanted electrodes has contributed to the exploration of the brain for structures involved in feeding behavior, aggression and penile erections. The question of whether or not the areas serving similar functions are neuroanatomically connected continues to be investigated. This year the study has involved the analysis of 12 additional brains using a modification of the Nauta-Gygax silver stain. First, additional evidence has been obtained for the existence of a two-way striate inferotemporal connection with a relay in prestriate cortex. Furthermore, interconnections have been found between the association cortices in the temporal, frontal, and parietal areas suggesting interaction among these areas during complex problem-solving. These interconnections had not heretofore been demonstrated.

Scientific Significance to Mental Health Research: Sufficient evidence has been accumulated in behavioral studies with brain-damaged animals to suggest that widely separated cell-aggregates, in cortex and subcortex, may be combined into a complex neural system; and it is the functioning of such complex neural systems, rather than the functioning of the particular elements of which they are composed, that seems most directly relevant to an understanding of the organization and disorganization of behavior. The significance of this project lies in the fact that it can provide detailed information on the composition of these neural systems.

Proposed Course of Project: No major shifts in emphasis are contemplated. Additional evidence will be obtained for the extrageniculate visual system, and for the interconnections between the association cortices. Increased attention will be paid to obtain evidence for the interconnections between the various structures involved in complex problem solving, in the maintenance of attention, and in the regulation of the E.E.G.

Part B included Yes ___ No X

Serial No. M-P-B-8
1. Laboratory of Psychology
2. Section on Animal Behavior
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Electroencephalographic correlates of sustained attentive behavior in man.

Principal Investigator: Allan F. Mirsky

Other Investigators: John Van Buren, Phillipe V. Cardon, Jr.

Cooperating Units: Surgical Neurology Branch, NINDB, Medical Neurology Branch, NINDB, Laboratory of Clinical Sciences, NIMH.

Man Years:
Total: 1
Professional: 1/2
Other: 1/2

Patient Days:
Total: 25

Project Description:

Project: Electroencephalographic correlates of sustained attentive behavior in man.

Objectives: This study is concerned with the relation between the E.E.G. and behavior on tasks requiring sustained attentiveness during periods of time of varying length. Both epileptic and normal individuals are studied. In the epileptic population, the primary interest is in the effect on behavior of hypersynchronous, and particularly paroxysmal epileptiform E.E.G. activity; in the normal subjects the primary interest is in study of the relationship between changes in the E.E.G. and behavior under those conditions in which attentive behavior is impaired. During the past two years, in collaboration with the other investigators listed above, the objectives of the study have been broadened to include simultaneous study of changes in autonomic functioning in addition to the analysis of the behavior and the E.E.G.

Methods: The technique involves simultaneous recording of a subject's performance on various types of visual, auditory, and simple motor tasks, the E.E.G., and up to seven different types of autonomic variables. The epileptic subjects are tested first on a standard combination of task parameters (i.e., stimulus duration, interstimulus interval and available response time) and then on variations of the parameters designed to elicit a high baseline level of performance during nonseizure intervals. The test equipment developed especially for this project facilitates greatly such

Part A.

Methods (Continued)

modifications of the task. Activation techniques such as hyperventilation and photic stimulation are frequently employed to increase the incidence of abnormal E.E.G. activity. The normal subjects are tested under control conditions and then under the influence of agents such as chlorpromazine and prolonged sleep deprivation which produce marked impairment in the subjects' ability to perform on these tasks.

Major Findings: Approximately 170 testing sessions to date have been conducted on epileptic patients of various diagnostic categories and on normal controls. The findings to date are presented in terms of the diagnostic category of patient or of the agent used (in the case of the normal controls) to produce impaired performance.

A. Epileptic patients with presumed subcortical (centrencephalic) pathology. Work during the past year has been devoted to scoring and coding E.E.G. and behavior protocols and in examining the relationships among the various classes of variables. The following relationships appear to have been established:

1) The majority of errors of omission made by petit mal patients on tests of sustained attention (either visual or auditory) occur in conjunction with spike and wave (s & w) episodes. As a group the eighteen patients studied to date make about 80% correct responses in the absence of bursts of s & w and about 25% correct responses in the presence of s & w.

2) Analysis of the time relations between errors and onset and cessation of the s & w burst has indicated that the errors precede the burst in time by several seconds (i.e., performance starts to fall before the seizure is manifest in the E.E.G.) and also that the performance begins to improve before the burst has ended.

3) Other analyses have indicated a relationship between the form of the burst and its effect on performance; bursts of the 'typical' three-per-second, bilaterally symmetrical, synchronous regular spike and wave variety shown by some patients tend to have more deleterious effects on behavior than those of the irregular, uneven, asymmetrical type shown by other patients. The fact that differences in the electrographic form of the seizure are accompanied by variations in the effects on behavior is suggestive of differences in the underlying pathology, and possibly, the locus of the disorder.

4) Tests of simple motor responding reveal a different time relationship to the burst than is evidenced by the more complex visual-motor or auditory-motor tasks described above. In the case of the simple motor response, the performance falters after the burst has become clearly manifest in the E.E.G., and not before. This suggests that the total impairment in 'consciousness' brought about by the central defect in petit mal epilepsy is in fact a process

Part A.

Major Findings (Continued)

which affects different levels of functioning at different time courses; possibly, the course of the seizure as here described reflects a downward spread of the epileptogenic process from central sensory way-stations to portions of the central motor pathways.

5) A system has been devised for coding all aspects of the behavioral, electrographic and autonomic features of the seizure thought to be relevant. It is hoped that all of the available test data will eventually be reduced to this form so as to permit further analysis of behavioral-physiological relationships of the kind described above.

B. Normal individuals under the influence of sleep deprivation and chlorpromazine administration. In this study comparison was made between the behavioral and physiological effects of 66 hours of sleep deprivation and of administration of 200 mg. of chlorpromazine in normal individuals. Although the behavioral effects are largely similar in that both agents produce major impairment in the ability to engage in sustained attention, the physiological concomitants of the impairment differ in the two cases. Errors after sleep deprivation are accompanied by marked E.E.G., respiratory and plethysmographic changes; those occurring with chlorpromazine administration are not. The existence of a dissociation between the behavioral and physiological effects of centrally-acting agents may be related to the temporal dissociation of the behavioral from the electrographic aspects of the petit mal seizure (see A2, 4 above). Both kinds of finding suggest that separate central neural systems may be involved in the maintenance of attentive behavior, on the one hand, and in the regulation of the E.E.G. (as well as other physiological functions) on the other. Research relevant to this concept might lead ultimately to a more accurate and precise localization of function within the central subcortical systems thought to be responsible for maintaining vigilance and regulating 'pacing' E.E.G.

C. The production of impaired consciousness by central stimulation in monkeys. In order to test directly the possibility that separate systems might exist for the control of attention and the E.E.G. (see B above), a project has been undertaken involving the training of monkey subjects to perform on a task similar to the one administered to the humans. After suitable criterion of mastery has been obtained the animals will be prepared for central stimulation through implanted electrodes. Simultaneous recordings will be made of behavior and E.E.G. changes with central stimulation in an effort to learn whether behavioral and E.E.G. 'impairment' may be produced independently, and to determine the loci of the central structures involved in such changes.

Scientific Significance to Mental Health Research: These studies suggest that

Part A.

Scientific Significance to Mental Health Research (Continued)

contrasting the behavioral and electrographic effects of agents or conditions which produce impaired consciousness may lead to a more complete understanding of the neural mechanisms and structures which maintain and mediate it. This research has suggested independent neural control of variations in attentiveness and of the E.E.G. changes that are thought to accompany them; this may be an important clue in localizing or characterizing the specific neural system responsible for maintenance of alertness, wakefulness and consciousness.

Proposed Course of Project: The major emphasis during the next few months will be in continuing the encoding and analysis of the data already obtained in the several experiments described above. The relationships among the several classes of variables (E.E.G., behavior, autonomic), as influenced by the several agents, will be studied in order to characterize more precisely the patterns of association.

In addition, attempts will be made to reproduce by brain stimulation in monkeys the various kinds of behavioral and electrographic effects observed in man. This research is designed to gain additional control of the variables and some much-needed precision with respect to the specific anatomical loci of the effects that have been studied in the epileptic, sleep deprived and chlorpromazinized human subject.

Part B included Yes ____ No X

Serial No. M-P-B 10
1. Laboratory of Psychology
2. Section on Animal Behavior
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Neural mechanisms regulating food and water intake. (Formerly: Hypothalamic mechanisms in hunger)

Principal Investigator: Bryan W. Robinson

Other Investigators: None

Cooperating Units: None

Man Years:
Total: 1
Professional: 1/2
Other: 1/2

Patient Days:
Total: None

Project Description:

Project: Electrode exploration for brain areas affecting food and water regulation.

Objectives: The principal purpose of this project is to map those areas in the forebrain and rostral midbrain of the macaque monkey from which ingestion and ejection of food and water may be directly evoked by electrical stimulation. Concurrently, observations are also made of evoked patterns related to other motivational systems, such as aggressive, defensive and sexual behavior.

Methods: Animals are prepared with a head-borne platform constructed in such a way that electrodes inserted through the platform and into the brain are oriented stereotaxically. In the unanesthetized animal the electrode is lowered through points 1 mm apart and the behavioral effect of stimulating each point is observed. The identification of the structures stimulated during this exploration is aided by monitoring changes in the electrode impedance as the electrode is advanced through the brain. At the conclusion of the exploration the electrode is returned to a point from which a desired behavioral effect has been obtained and fixed in place. It is then used for chronic studies involving stimulation, recording, and conditioning. Many electrodes are lowered in the same animal and the location of the electrodes are verified later by histological techniques. Thus it is possible to locate precisely all the neural structures from which a particular behavioral pattern was evoked electrically.

Part A.

Major Findings: To date approximately 3000 points have been stimulated in seven animals. The principal findings are: (1) In addition to the expected pattern of food and water ingestion, a well-defined pattern of food-ejection has been evoked many times in several animals. (2) Each of the patterns of water and food intake and ejection can be evoked not only from hypothalamus, as described by others, but also from a widespread system probably including the orbito-frontal cortex, olfactory tubercle, substantia innominata, amygdala, septum, and rostral tegmemtum.

Scientific Significance to Mental Health Research: It is felt that a neuro-psychological analysis of basic motivational systems such as feeding, defense, aggression, and sex in the monkey will contribute materially to the understanding of the basic substrata of human behavior.

Proposed Course of Project: To continue with the methods outlined, exploring additional points in other animals.

Part B included Yes X No ___

Part B. Honors, Awards, and Publications

Publications other than abstracts from this project:

MacLean, P. D., Robinson, B. W., and Ploog, D. W.: Experiments on localization of genital function in the brain. EEG J. 12: 749, 1960. (Also reported from Section on Limbic Integration).

MacLean, P. D., Robinson, B. W., and Ploog, D. W.: Experiments on localization of genital function in the brain. Trans. Amer. Neurol. Ass. 105-109, 1960. (Also reported from Section on Limbic Integration)

MacLean, P. D., Ploog, D. W., and Robinson, B. W.: Circulatory effects of limbic stimulation, with special reference to the male genital organ. Physiol. Rev. 40: 105-112, 1960. (Also reported from Section on Limbic Integration)

Robinson, B. W.: Book review of Ashby, W. R. Design for a Brain. J. Neurophysiol. 1960, vol, 24. (In press)

Serial No. M-P-B-11
1. Laboratory of Psychology
2. Section on Animal Behavior
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Physiological and behavioral correlates of a neural alimentary system.

Principal Investigator: Bryan W. Robinson

Other Investigator: None

Cooperating Units: None

Man Years:
Total: 1-1/2
Professional: 1/2
Other: 1

Patient Days:
Total: None

Project Description:

Project: Correlation between alimentary reflexes and other psychophysiological phenomena evoked by forebrain stimulation.

Objectives: The principal purpose of this project is to investigate the autonomic and motivational effects of stimulating the neural structures in the forebrain which regulate food and water intake.

Methods: The animals used for the mapping study in Individual Project Report No. M-P-B-10 are prepared with chronic electrodes, placed in a restraining chair, and subjected to the following physiological and behavioral investigations: (1) At each chronic point a record of evoked changes in respiration and heart rate is obtained, along with other indicators of autonomic activity. Each point is classified as sympathetic, parasympathetic, or mixed, and is ranked on an intensity scale. (2) Each point is evaluated as to whether or not it will motivate self-stimulation and/or escape from stimulation, and is ranked on an intensity scale along each dimension. (3) Points which produce the same or different alimentary reactions are stimulated simultaneously to investigate the nature of the interactions, if any. Further, interaction is studied between those loci evoking alimentary reflexes and those evoking other behavioral patterns related to aggression, defense, sexual activity, etc. Facilitation, inhibition, and other changes are noted and these also are ranked on an intensity scale. (4) Selected points are used for classical conditioning experiments, with the brain stimulation as the UCS.

Major Findings: Approximately 80 points (in seven animals) have been

Part A.

Major Findings (Continued)

investigated thus far in the first three studies comprising this project. While these preliminary data look promising, it appears that the final pattern of correlations will be complex, indicating that many more points must be studied before any conclusions are drawn. In the fourth part of the study attempts to classically condition three centrally evoked patterns of behavior in two animals have met with moderate success. In the first of these, the somatic motor concomitants of a weak feeding point were conditioned to a tone, but food ingestion was not conditioned; in the second, a penile erection was conditioned to a tone, but the conditioned erection was most prominant during extinction; and in the third, still in progress, an aggressive pattern consisting of characteristic leg and arm stancing and shaking of the chair has been conditioned to an interrupted tone. These later results have indicated that the failure to obtain conditioned food ingestion from the first point may have been due to premature termination of the conditioning. A water ingestion point will be investigated next.

Scientific Significance to Mental Health Research: Analysis of the physiological and psychological correlates of well-defined alimentary and other consummatory responses in animals will contribute materially to our understanding of the emotional and motivational systems that are important in mental health.

Proposed Course of Project: The study is only in the early phases of data-gathering, and many more points must be investigated using the methods outlined above. In addition, attempts will me made to design and construct apparatus for long-distance stimulation and recording, thereby permitting study of the effects of stimulation in the unrestrained, socially interacting animal.

Part B included Yes ___ No X

Serial No. M-P-L-1 and M-P-L-1 (a)
1. Laboratory of Psychology
2. Section on Perception and Learning
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Effects of Lysergic Acid Diethylamide (LSD-25) on Visual Functions

Principal Investigator: V. R. Carlson

Other Investigators: Eugene Tassone
William Jones

Cooperating Units: Laboratory of Clinical Science, NIMH

Man Years
Total: 1.16-2/3
Professional: .33-1/3
Other: Research Assistants: .66-2/3
Secretarial: .16-2/3

Patient Days
60 In-patients

Project Description:

Objective: LSD produces various subjectively described distortions in visual experience. These and other symptomatic effects have been likened to psychotic conditions. For the purpose of this experiment, however, the degree to which this drug may duplicate psychotic behavior is not of crucial importance. Rather, it is presumed that the psychological state engendered by LSD is one of heightened attention to and preoccupation with subjective experience, especially that of sensory character. The purpose of the experiment is to determine whether, under these psychological circumstances, size constancy judgments are significantly altered, and, if so, whether in the direction of over- or under-estimation of size-at-a-distance.

Methods Employed: On one day 75 μg. of LSD, and on another day placebo, was administered to normal volunteer subjects. One group received LSD on the first occasion, another group received placebo first. The principal task, size constancy, requires the subject to equate the size of a variable triangle at 10 ft. to the size of a

Part A.

Methods Employed (Continued):

standard triangle at 40 ft., under normally good conditions for distance perception. Instructions specified a match in terms of apparent visual size. Since requiring distance judgments might affect the size judgments, one group of subjects made only size judgments and a second group made both size and distance judgments.

Besides perceptual effects, LSD also produces changes of a more purely optical nature--principally pupillary dilatation and perhaps some effect on accommodation. Measurements of visual acuity and related visual factors were also obtained under both of the experimental conditions.

Major Findings: There was no clear overall difference in the size-constancy judgments between the LSD and placebo conditions. Those subjects who received LSD first, however, tended significantly to underestimate size-at-a-distance in both the LSD and placebo conditions, while those subjects who received placebo first did not, on the average, deviate significantly from an objectively equal size-match in either condition. These results are in agreement with prior preliminary findings which had been obtained less systematically. These findings cannot be interpreted in terms of a drug effect upon the perceptual process itself but require, rather, an hypothesis of effect upon an attitudinal, or response, bias.

LSD produced a consistent, but slight, impairment in visual acuity. This effect was not significantly different, however, for the two groups of subjects and therefore does not account for the effects on size judgment.

Scientific Significance to the Program of Mental Health Research: Current theoretical orientations in perception generally derive perceptual phenomena such as size constancy from supposedly more basic sensory processes. The formulation underlying the present experiment, however, is that perceived object size is, fundamentally, invariant with variations in perceived distance and deviations from this relationship are brought about through the operation of learned attitudes about size-distance interactions. The question whether immediate visual experience represents underlying sensory processes more directly than do so-called perceptual responses is an issue with considerable imlication beyond the particular problem of size constancy. It is important both in formulating a sound theoretical account of normal perceptual functioning and in achieving an adequate interpretation of aberrant perceptual manifestations.

Part A.

Proposed Course of Project: No further experimentation with LSD is contemplated at the present time.

Part B. included: Yes

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B. Honors, Awards, and Publications

Publications other than abstracts from this project:

Carlson, V. R.: Effects of sleep-deprivation and chlorpromazine on size-constancy judgments. Accepted for publication in Amer. J. of Psychol.

Honors and Awards relating to the project: None

Serial No. M-P-L-2

1. Laboratory of Psychology
2. Section on Perception and Learning
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Test of the Satiation Theory of Perception

Principal Investigator: V. R. Carlson

Superseded by Project number M-P-L-7 as of January 1, 1960

Serial No. M-P-L-5
1. Laboratory of Psychology
2. Section on Perception and Learning
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Individual Differences in Normal Perceptual Processes

Principal Investigator: V. R. Carlson

Other Investigators: Eugene Tassone
William Jones

Cooperating Units: Section on Aging, Laboratory of Psychology, NIMH

Man Years
Total: 1.16-2/3
Professional: .33-1/3
Other: Research Assistants: .66-2/3
Secretarial: .16-2/3

Patient Days
200 out-patients

Project Description:

Objectives: (1) To obtain normal control data for standardizing procedures and apparatus in the measurement of perceptual variables, and to obtain comparison data for evaluating the effects of drug and other abnormal conditions. (2) To develop a general specification of perceptual response in terms of the following determinants: parameters of the immediate sensory stimulus-complex and their dependence upon past experience, generalized perceptual-cognitive attitudes, and the subject's motivational reaction to the situation.

Collection of data, begun last year, on the size-constancy performance of older normal subjects is being continued. Availability of these subjects, however, has not yet permitted a sample sufficiently large for proper analysis.

Part A.

Objectives (Continued):

Work with younger normal subjects this year has been directed toward determining whether overconstancy, produced by an attitudinal bias on the part of the experimental subject, can occur to as great an extent as underconstancy.

Methods Employed: The size-constancy judgment is one of equating two objects with respect to size when the objects are presented at different distances in a situation providing good depth perception. An instruction was devised to make explicit the attitudinal bias--referred to here as the perspective attitude--postulated to be operating when a subject is asked to make a size-match of objective equality. There is, however, no basis in logic or in the immediate stimulus-situation for a judgment of such 'perspective size' to be any different from a judgment of 'objective size'. If a difference does occur, therefore, it must be due to an attitudinal bias on the part of the subject. Judgments of 'projective size' were also obtained from the same subjects. Projective size is defined in terms of geometrical angular size and specifically requires that a nearer, smaller object be equated to a more distant, larger object (underconstancy).

Major Findings: The perspective-size instruction clearly produced a greater degree of overestimation than objective-size instructions. The deviation from a correct match in terms of equal physical size was approximately the same as the deviation in the opposite direction produced by projective-size instructions. This result provides strong support for the hypothesis that size-constancy represents the basic functional relationship between object-size and perceived size, and deviations from this relationship are produced by extra-perceptual response-biases.

Scientific Significance to the Program of Mental Health Research: Current general views of perception conceive of perceptual functioning in terms of a kind of analogy to the operation of a computer, in which a perceptual result is achieved from inferences based on sensory cues. The present argument derives from a fundamentally alternative theoretical orientation, which identifies certain operational specifications of sensory cues as based essentially upon non-perceptual factors. In the case of size constancy the specific question is whether the angular size of the retinal image constitutes a sensory cue; but the issue goes beyond the problem of perceptual constancy, having important general implications for theories of perception.

Part A.

Proposed Course of Project: This project is an indefinitely continuing one in pursuance of the general objectives stated above.

Part B. included: Yes

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B. Honors, Awards, and Publications

Publications other than abstracts from this project:

Carlson, V. R.: Overestimation in size constancy judgments. Amer. J. Psychol. 73: 199-213, 1960

Honors and Awards relating to the project: None

Serial No. M-P-L-6
1. Laboratory of Psychology
2. Section on Perception and Learning
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Environmental and Genetic Variables Affecting Biological Systems

Principal Investigator: John B. Calhoun

Other Investigators: Kyle R. Barbehenn (NIMH Post Doctoral Fellow)
Robert Wilson
John Kline

Man Years
Total: 4.50
Professional: 1.00
Other: Post Doctoral Fellow: 1.00
Research Assistant: 1.00
Animal Caretaker: 1.00
Secretarial: .50

Patient Days
None

Project Description:

Objectives: The ultimate aim is to develop principles of structuring the physical and social environment within which a social organization may develop that permits an optimum expression of the individual's genetically determined capacities. Where single individuals or small groups are utilized in highly simplified conditions, these experiments are considered not as ends of themselves, but as means toward a fuller appreciation of the processes characteristic of organized groups in complex situations.

Methods Employed: Wild and domesticated strains of rodents and shrews are subjects. (Note: Methods Employed, Major Findings, and Scientific Significance to the Program of Mental Health Research sections are subdivided into areas of specific endeavor although their logical interrelationships are such that they must be considered as a single project).

Part A.

Methods Employed (Continued):

Area 1. Social Organization of Animals Living in their Natural Habitat

The resident community is removed by long-term continuous trapping. In some studies trapping is preceded by modifying the social organization of existing populations through the placing of fixed food hoppers at appropriate locations.

Area 2. Emotional Hyperactivity.

Rats with varying backgrounds were given two-hour exposures to a strange situation, a fifteen foot alley, where they had the choice of avoiding this field or entering it. If they entered, the total activity during each of eight successive fifteen minute periods was recorded.

a. Experimental: Subjects consisted of sixty-four rats, each shielded for six months after weaning from opportunity to adjust to environmental changes. These "isolated" rats were then divided into four groups, each of which was given ten 2-hour training trials of adjusting to environmental change. Degree of environmental change varied across these groups. The test situation involved four alleys varying in degree of strangeness from their prior experience. Four rats from each training group were given four 2-hour trials in one of the four alley conditions. This 4 x 4 training test matrix comprised the experimental design.

b. "Clinical": Rats living under the dietary and social environmental conditions outlined under Area 3 of Methods Employed are removed, given two-hour alley trials and returned.

Area 3. Vitamin A and Social Stress.

Rats are being reared in two major settings. One (the controls) confines one male and two females to a small pen, the other permits the development of large social groups consisting of approximately eighty adults. In each setting groups are provided with identical diet except that the Vitamin A content is either 3, 6, or 12 units per gram.

Part A.

Major Findings:

Area 1. Social Organization of Animals Living in their Natural Habitat

(These findings are based upon field studies conducted by Dr. Barbehenn or by other workers across the continent who collaborated with us in the design of their study). Only two particularly noteworthy findings will be mentioned: 1. Some species of mice and shrews develop loose communication networks, having a mean of twelve members. 2. Whereas, most species of small mammals inhabiting any particular habitat become integrated into an inter-specific social communication network, the behavior of the genus Microtus indicates that it is unaware of this communication network in which its neighbors are enmeshed.

Area 2. Emotional Hyperactivity.

a. Experimental: This study amply demonstrated that (1) the fewer were the prior opportunities for adjusting to the strange stimuli the greater the avoidance of the test field, and (2) for those rats which entered the test field, the more the strange stimuli the longer the state of hyperactivity persisted.

b. "Clinical": The following table is based upon 312 two-hour trials so far run:

Proportion of Rats which Avoid Entering Alley

Vitamin A. Content of Diet	Size of Social Group	
	Small	Large
Low	.48	.06
High	.40	.36

Area 3. Vitamin A and Social Stress.

Ability to rear young serves as the best index of the degree to which environmental conditions disrupt behavior. The incidence of pregnancies has so far been nearly identical in all groups. However, some females desert their young:

Part A.

Major Findings (Continued):

Number of Young Reared to
a Median Age of Ten Days

Vitamin A. Content of Diet	Size of Social Group	
	Small	Large
Low	336	295
High	153	129

Because of the different number of females involved comparisons at present are justified only between diets, within a group size. Later it will be possible to make exact comparison between group sizes in terms of young reared per female. However, qualitative analyses so far indicates that maternal behavior among females in large groups is much more disrupted then among those in small groups.

Marked fighting continually characterizes the large social group on a low Vitamin A diet (i.e. 3 I.U./g), and yet the females there are remarkably successful with regard to conception, and those maternal behaviors necessary to rear young to weaning. In contrast the members of the large social group on a high Vitamin A diet (i.e. 12 I.U./g) fight very little, and yet even in the absence of this social stress many indications of disrupted maternal behavior exist.

Scientific Significance to the Program of Mental Health Research:

Area 1. Social Organization of Animals Living in their Natural Habitat

These field studies support the developing theory that the physics of the social use of space fixes optimum group size at near twelve individuals. Furthermore, the data concerning the mouse, *Microtus*, suggests that where contact rate customarily rises above the level characterizing a group of twelve, there must be compensatory evolution enabling the species to ignore signals emanating from its associates.

Part A.

Scientific Significance to the Program of Mental Health Research (Con't):

Area 2. Emotional Hyperactivity.

a. Experimental: These findings indicate that ability to adjust to exigencies of the environment requires prior experience in making such adjustments. Furthermore, if the current required adjustment represents a marked change from a prior state, the probabilities are high that no behavioral adjustment will follow despite repetitive opportunities for making an adjustment.

b. "Clinical": At the present time all we may conclude is that socially stressful conditions coupled with physiological changes induced by a high Vitamin A diet appears to alter ability to adjust to environmental change.

Area 3. Vitamin A and Social Stress.

Both diet and group structure alter behavior. We have long been aware that group structure can alter behavior, however, the findings of this study to-date suggest that a single dietary component, varying only within the range considered as "normal" may also drastically alter behavior.

Proposed Course of Project: Dr. Barbehenn is initiating a study of the comparative biology of the vocalizations and ability to perceive auditory signals among mice and shrews, for which field studies indicate vocalization and audition serve as the means through which both intra-specific and inter-specific social organization develops. Dr. Calhoun will devote calendar year 1961 to completion and analyses of the current project on Vitamin A and social stress.

Part B. included: Yes

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B. Honors, Awards, and Publications

Publications other than abstracts from this project:

Calhoun, J. B.: A behavioral "sink". (Accepted for publication).

Honors and Awards relating to the project: None

Serial No. M-P-L-7
1. Laboratory of Psychology
2. Section on Perception and Learning
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Perceptual Adaptation

Principal Investigator: V. R. Carlson

Other Investigators: Eugene Tassone
William Jones

Cooperating Units: Dr. Irwin Feinberg, Clinical Neuropharmacology Research Center, NIMH

Man Years
Total: 1.16-2/3
Professional: .33-1/3
Other: Research Assistants: .66-2/3
Secretarial: .16-2/3

Patient Days
500 In-patients
300 Out-patients

Project Description:

Objective: To explore the fundamental bases of perceptual adaptational processes. The present experiments are concerned primarily with determining whether adaptation to perceived motion is formally analogous to color and temperature adaptation.

Methods Employed: A test of perceived velocity was developed especially for this project. In this test the subject sees a test line move across an aperture and disappear. He responds when he judges the line would coincide with a target presented further along in the trajectory. Response-time is taken as a correlate of the perceived speed of the line. In order to study the effects of adaptation, a moving pattern is presented in the aperture for a period of time preceding the test trial. The adaptation pattern moves at the same speed or faster or slower than the test line and in either the same or opposite direction.

Part A.

Methods Employed (Continued):

The response of schizophrenic patients to this perceptual velocity test is also being explored. Here the interest is in a progressive change in response-time over an extended period of practice on the test. The patients are required to respond to presentations of the test line a number of times once a week for twelve weeks.

Major Findings: A clear aftereffect of adaptation to the pattern occurred when the test line was moving in the same direction and at a slower speed relative to the adaptation pattern. There was some indication of effect when the test line moved in the same direction and at a speed equal to or greater than that of the adaptation pattern. There was no effect when the test line and adaptation pattern moved in opposite directions. These results are only partially in agreement with the kinds of adaptation effects obtained in color and temperature perception.

Preliminary results with schizophrenic patients, on the velocity test alone, suggest that these subjects develop abnormally long response-times with extended repetitions of the task. In spite of the extraordinarily long latencies, however, responses appear to vary appropriately with variations in the stimulus-parameters of the task.

Scientific Significance to the Program of Mental Health Research: More and more, findings in the field of perceptual adaptation suggest that normal perception is a conditioning-adaptational process continuously dependent upon ongoing stimulation. At the present time adaptational effects are evident in a number of different kinds of experimental situation, but there appear also to be some crucial differences among them. It is highly probable that any general theory of perception will have, at the least, to give a satisfactory account of these adaptation phenomena, and may well have to accord them a position of central importance.

Proposed Course of Project: The procedures presently worked out will be refined and extended. A number of specific variables require further exploration.

Part B. included: No

Serial No. M-S-D-1
1. Socio-environmental Studies
2. Social Developmental and Family Studies
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: The Formation of Children's Peer Relationships

Principal Investigators: Marian Radke Yarrow and John D. Campbell

Other Investigators: None

Cooperating Unit: Family and Child Services, Washington, D. C.

Man Years (calendar year 1960):		Patient Days (calendar year 1960):
Total:	1-1/4	
Professional:	3/4	None
Other:	1/2	

Project Description:

Objectives: Investigations of environmental influences upon child personality and behavior have rarely given attention to the child's perceptions and understanding of the experiences to which he is exposed, particularly in regard to the human environment. The problem to which the present research is directed is one of determining the nature of the child's sensitivities to the characteristics and motives of persons with whom he interacts, and the nature of his causal inferences about interpersonal relationships. This investigation has turned to three interrelated issues: (a) developmental aspects of cognitive processes, (b) situational and social correlates of children's interpersonal perceptions and (c) the interaction of cognitive and behavioral factors in establishing social relations.

Methods Employed: Two hundred sixty-seven preadolescent children from low income families were studied in summer camps. Children were assigned to cabin groups homogeneous in age and sex. They were then interviewed and observed in initial and later phases of a two-week camp period. Using open-ended, sociometric, and projective questions, interviewers obtained children's impressions and judgments regarding their peers, their adult leaders, and their self-images. Detailed observations of behavior were recorded using a time-sampling procedure.

Major Findings: In the project report for calendar year 1959, findings concerning the ways in which age-developmental factors, sex typing, and behavioral factors function in shaping interpersonal relations have been summarized. In the past year the relation between personality factors and cognitive approaches has been singled out for analysis.

(1) Information about a child's personality does not permit accurate prediction of the descriptive categories that child will use in reporting his impression of another. But the quality of such descriptions is linked to the child's personality: Children who are more adequately adjusted to the social situation in which they are functioning (as measured by peer appraisals, by behavioral indices, and by adult leaders' ratings of personal characteristics) tend to organize and interpret their impressions of others in a fashion superior to that of children who are less adequately adjusted.

(2) Perceptual selectivity in children's appraisals of persons is markedly influenced by interpersonal affect. For example, the actual disruptive social behavior of a well-liked child is not apt to be reported in peer descriptions; yet such disruptive behavior is "seen" as prominent in a less well-liked child who, in terms of objective behavioral indices, in fact displays a small amount of such interaction.

(3) A methodological by-product of this study, an investigation of intermeasure correspondence in appraisal of social relations has been undertaken. Three different sources (children's assessments of one another, adults' ratings of the children, and research observers' records of interaction) provided data on which to compare selected measures of status and individual functioning. A wide variation in degree of intermeasure correspondence appears: For some variables (e.g., measures of general status, such as popularity) a considerable degree of intermeasure correspondence was obtained. For others (e.g., appraisal of anxiety and its behavioral manifestations) considerable intermeasure discrepancy existed. Instituting appropriate statistical controls in some instances markedly increased the degree of correspondence between measures.

Scientific Significance: While developmental theory has been very concerned with the effects of childhood experience upon subsequent personality and behavior, little inquiry has gone into the accompanying cognitive processes of the child. By the traditional approach it has been

possible to account for only part of the variance in outcome. Possibly we can fill in our theories by acquiring sensitivity to cognitive aspects of child experience. Knowing what children perceive in other persons (peers and adults) may contribute to further understanding and to prediction and control of interpersonal influences on children.

The general methodological question, do presumed alternative measures of the same social-psychological phenomena lead to the same results in appraisal of data, has rarely been studied. Techniques of the present investigation permit a comparison of several such alternative measures. Knowledge of intermeasure correspondence or its lack may help both to improve techniques for measuring and also to clarify certain issues centering on interpretation of the meaning of such measures.

Proposed Course of Project: A report on "Perceptual and Behavioral Correlates of Social Effectiveness" has been submitted to a professional journal for publication. Data have been analyzed and a final draft of a report on "Children's Perceptions of Persons" is now being prepared for publication. Preliminary analyses for a paper on "Intermeasurement Correspondence in Appraisal of Children's Social Relations" have been completed, and a paper on this topic is currently being written.

Part B included Yes [x] No [ ]

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B: Honors, Awards, and Publications

Publications other than abstracts from this project:

Yarrow, Marian R. "The Measurement of Children's Attitudes and Values," in Handbook of Research Methods In Child Development, Editor, Paul Mussen, New York, John Wiley and Sons, 1960.

Honors and Awards relating to this project:

None

Serial No. M-S-D-3
1. Socio-environmental Studies
2. Social Developmental and Family Studies
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: The Validity of Retrospective Data on Parent-Child Relationships

Principal Investigators: Marian Radke Yarrow and John D. Campbell

Other Investigators: Doris E. Hawkins and Roger V. Burton

Cooperating Unit: National Child Research Center, Washington, D. C.

Man Years (calendar year 1960):		Patient Days (calendar year 1960):
Total:	2-3/4	
Professional:	3/4	None
Other:	2	

Project Description:

Objectives: This project, primarily methodological in focus, is an investigation of the nature of parents' retrospective reporting on events and conditions pertaining to the earlier development of their children. The aims of the investigation are specifically: (1) To assess the nature of differences between earlier events and parents' recollections of such events. (2) To determine how retrospection is influenced by such factors as the time interval between events and recall, intervening events, and current social psychological situation.

Methods Employed: Approximately two hundred and fifty mothers of children on whom data were collected two to twenty-five years ago are now being interviewed. Their child's sex, current age, and position in birth order are factors on which a systematic sampling of mothers has been based. The interviews obtain mothers' retrospective reports concerning specific aspects of child development and parent-child relationships. Data from these interviews will be compared with a baseline consisting of direct observations, interviews, and ratings gathered at the earlier time. Such comparisons will permit assessment of the degree of reliability of such retrospective reports. Since an interview on recall alone would pose special problems with

regard to interviewee rapport and understanding of the research objective, special attention has been given to the formulation of the research instrument. The interview schedule as developed imbeds items on maternal recall in the context of a study of the maternal role and parent-child relations throughout the childhood period.

Major Findings: Data collection is about 5/6 completed. Final coding and analysis procedures are in process of being developed. There are no findings to report at this stage.

Scientific Significance: Examination of the nature of the retrospective process is of importance in the development of a science of personality development. The technique of recall has considerable prominence among the techniques of research used in investigating the significance of childhood experiences for later development. Most often the parent is asked to reconstruct his precepts and practices in caring for his child or to describe the characteristics of his child as of some designated earlier period. Research findings using this method have obtained trends and tendencies but have not contributed large or powerful increments to knowledge as to differential etiologies of pathologies or normality.

Proposed Course of Project: The work of the past year has been essentially a continuation of the activities described in the project report for calendar year 1959. Systematic abstracting of baseline records and interviewing of mothers are proceeding concurrently. This process of data collection requires a considerable expenditure of time and effort. Abstracting information from baseline records and completing an interview with a mother together require more than eight hours per case. It is anticipated that interviewing will be completed in approximately three months. Some of the methodological issues in formulating and applying basically identical qualitative coding schemes to data deriving from two different sources (case records and retrospective reports) have been considered. Completion of the tasks of abstracting case records and development of analysis procedures will serve as a major goal for this project during the coming year.

Part B included Yes [ ] No [x]

Serial No. M-S-D-4
1. Socio-environmental Studies
2. Social Developmental and family Studies
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Life Styles in Aging

Principal Investigator: Marian Radke Yarrow

Other Investigators: None

Cooperating Units: Laboratory of Clinical Sciences, Laboratory of Psychology, and Social Service Department, NIMH

Man Years (calendar year 1960):		Patient Days (calendar year 1960):
Total:	3/4	
Professional:	1/4	None
Other:	1/2	

Project Description:

Objectives: This project is part of a larger research project on the functioning of physically healthy aged persons which brings the perspectives and measurement of physiology, psychiatry, psychology and sociology to the examination of factors in human aging. This report concerns social psychological aspects of aging. The research questions are: (1) Where inroads of physical and psychiatric pathology are minimal, how is old age lived? Specifically, what are the activities, interests, and aspirations that make up day-to-day living? (2) To what extent are life-history variables predictive of functioning in old age? (a) To what degree do earlier patterns of living and interpersonal relationships change or carry over into old age? (b) Are earlier modes of coping with life problems appropriate to the problems of old age? (3) How much are behavior and attitudes of the aged person a function of his current environmental circumstances?

Methods Employed: Physically healthy male subjects were brought to the Clinical Center for two weeks of intensive study by investigators from several cooperating Laboratories. For the social psychological study within the larger interdisciplinary project, data were obtained through a series

of interviews, two of which were conducted while the subject was living at the Clinical Center, a third with the subject in his home about a month later and a fourth with a person chosen by the subject who has known him over a long period of time. In addition, systematic observations of the subjects were made by the nursing staff on the ward and by a sample of investigators.

Major Findings: In the annual report of 1959, findings on the social functioning of this sample of aged men were reported. Below are reported correlations between these social variables and tested cognitive functioning, physiological measures and psychiatric assessment.

1. There are significant relationships between environmental losses (mainly losses of love-objects) and (a) psychiatric assessments of depression and (b) subject's self-reported reclines.

2. Measures of the adequacy of present psycho-social functioning (including measures of complexity of daily behavior, attitudes, goals, social contacts, relationships with family) show significant relationships with the following variables:

   (a) Tests of cognitive functioning. Lower cognitive scores are associated with less adequate social functioning.
   (b) Subjects' self-reported declines. Age-associated declines are reported more frequently by men rated as functioning less adequately socially.
   (c) Reaction time. Poorer social functioning is associated with slower reaction time scores.
   (d) Depression. Depressive trends (on the MMPI) are linked with less adequate social functioning.
   (e) Cerebral metabolism. Lower scores on measures of cerebral blood flow, cerebral oxygen consumption and glucose consumption are associated with the poorer scores on social functioning.

Scientific Significance: Ours is a population in which the proportion of elderly people is steadily increasing. Research on the aging process and the role of the aged in our society is much needed in many areas of service, such as medicine, social work, institutional planning, employment practices, and community services. An important characteristic of the present research is that it studies healthy aged persons, whereas the bulk of gerontological research has dealt with sick or institutionalized aged subjects. These data should contribute to an understanding of develop-

mental processes at the end of the life cycle.

Proposed Course of Project: The preparation of a book, "Biological and Behavioral Aspects of Human Aging," will be completed within the calendar year. The book will be published in 1961 by the GPO. The following chapters have been contributed to this publication (some with joint authorships with members of the other cooperating laboratories):

Human Aging, Introduction (joint authorship)
Social Psychological Aspects of Aging
Intercorrelations of Physiological Psychological, Psychiatric and Social Variables in Aged Men (joint authorship)
Summary and Conclusion (joint authorship)

Other publications indirectly from this project:
The Appraisal of Environment, to appear in published report of the International Research Seminar in Gerontology, held in San Francisco, August 1960.

Part B included: Yes [x] No [ ]

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B: Honors, Awards, and Publications

Publications other than abstracts from this project:

Yarrow, M., P. Blank, O. Quinn, G. Youmans, J. Stein, "Social Psychological Aspects of Aging"

Birren, J., R. Butler, L. Sokoloff, M. Yarrow, "Human Aging, Introduction"

"Intercorrelations of Physiological, Psychological, Psychiatric and Social Variables in Aged Men"

"Summary and Conclusion"

Chapters in Biological and Behavioral Aspects of Human Aging, to be published by the Government Printing Office, 1961.

Yarrow, M. R., "The Appraisal of Environment," to appear in published report of the International Research Seminar in Gerontology, San Francisco, August 1960.

Honors and Awards relating to this project:

None

Serial No. M-S-D-7
1. Socio-environmental Studies
2. Social Developmental and Family Studies
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Research on Methods of Assessing Interpersonal Relationships within the Family

Principal Investigators: Thomas L. Gillette and Marian Radke Yarrow

Other Investigators: None

Cooperating Units: None

Man Years (calendar year 1960):		Patient Days (calendar year 1960):
Total:	$\frac{1}{4}$	None
Professional:	$\frac{1}{4}$	
Other:	-	

Project Description:

Objectives: To develop techniques of investigating relationships within the family, particularly within the family's natural setting. The interview has remained the primary approach in family research. With this technique, research has advanced our knowledge in areas of parent-child relations, personality development as it relates to experiences in the family, and family dynamics in general. Increasingly, however, research workers of very different orientations have become dissatisfied with sole reliance on the interview. At the present stage of research, advances would seem to depend very much upon advances in methodology. The investigation and development of observational methods is viewed as one avenue by which other, possibly better, data and concepts on family relationships may be obtained.

This methodological objective represents a continuing research interest in the Section. It is being advanced through a series of small exploratory studies, which are intended to clarify various issues in observational methods before a major project is designed employing observational techniques.

Methods Employed: One preliminary project was aimed at a comparison of data obtained on a small group of families through questionnaires, interviews, and direct observation. This project (carried out by Gillette) investigated the areas of power structure, authority, and division of responsibilities within the family. Ten families were studied. Observers lived in the families as quasi-family members. Students participating in an international exchange program were utilized as the observers. In addition to observational data, questionnaires and interviews were administered to family members at successive stages before, during and after the participation by the student-observer.

Major Findings: Analysis has not been completed. Analyses of parts of the data show that inconsistencies in family behavior, variations in manner of decision making and discipline within the family are more visible in the observations than in the questionnaire and interview data from these families.

Scientific Significance: The fundamental importance of the family in influencing development and behavior is well recognized and documented. Methods of obtaining family data have various liabilities and assets, the clarification of which would add substantially to the value of research on the family. This may be especially true of observational methodology which, although yet relatively unrefined, has recently offered great promise.

Proposed Course of Project: Relatively little time has been given to this project in the past year. As the related Project M-S-D-8 is completed, analyses on this research will proceed. This study is one from which there should be indications for next steps of research into observational studies of family relations.

Part B included Yes [ ] No [x]

Serial No. M-S-D-8
1. Socio-environmental Studies
2. Social Developmental and Family Studies
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Research on the Mother Role

Principal Investigators: Thomas L. Gillette and Marian Radke Yarrow

Other Investigators: None

Cooperating Units: American Association of University Women

Man Years (calendar year 1960):		Patient Days (calendar year 1960):
Total:	2	None
Professional:	1	
Other:	1	

Project Description:

Objectives: This research is part of a series of projects on methodological problems in the study of family relationships. We are investigating variations in the mother role, with an emphasis on the mother's personal goals in her various adult roles (wife, career, woman) and their relation to family functioning and child-rearing. This project consists of several interrelated studies:

Study 1: This portion of the study is concerned with some of the roles carried out by the mother in American society. The primary interest here is in differences occurring between working and non-working mothers, and the relationship of these differences to social class and racial membership. That complex of attributes defined as social class probably results in strikingly different "life styles" for women living at various levels of the social structure. These life styles are undoubtedly influenced by racial membership and maternal employment status. We are interested in how differing combinations of these statuses (social class, race, maternal employment) operate to influence (1) the differential degree and type of family member

participation in household tasks, (2) the mother's concept of self and her satisfaction with certain combinations of roles, (3) her evaluation of maternal employment and motives for working or not working outside the home, and (4) consensus between husband and wife on family norms.

Study 2: This study is concerned with the influences upon socialization of children of differences in mothers in regard to their social roles and ideologies as women. (a) How does maternal employment or non-employment influence child-rearing? (b) How do differences in mothers' attitudes regarding male and female roles influence child rearing?

Methods Employed: In Study 1, questionnaires were used in collecting data from 700 mothers from various social class levels in the metropolitan Washington, D. C. area. In Study 2, a sub-sample of 50 sociologically matched pairs of mothers (working and non-working) was drawn from the larger sample. Interviews were used with this sample.

Major Findings: Study 1: Based on the questionnaire data, differences in attitudes toward maternal employment seem to be more striking between working class and middle class mothers than between working and non-working mothers within either given social class. Middle-class mothers seem to view working as a way of furthering their own personal development (self-oriented) while working class mothers see it as something which improves the level of family living (family-oriented). Regardless of social class status, Negro women in general have a more positive orientation toward maternal employment than do white women. For example, the Negro women are more apt to have held the pre-marital expectation of combining motherhood with working. Negro mothers are also less likely to see working and child rearing as being incompatible, and more likely to indicate dissatisfaction if they are not employed outside the home.

Differences which occur among social classes in family role performance are accentuated by controlling for maternal employment status. While middle class fathers are more likely to share in household functions than are working class fathers, the husbands of working mothers in both social classes are more active than men whose wives do not work. Middle class mothers also report more often that they know their husband's attitudes

on a variety of family-oriented issues, and that their husband's attitudes concur with their own. In contrast, working class mothers more often indicate that they do not think they know how their spouses feel about certain areas of family life--or if they do know, they more often indicate a discrepancy between their own and their husband's point of view. Again, in controlling for maternal employment status, sharper differences occur. For example, within a given social class, working mothers are more likely to indicate knowledge about and concurrence with spouse's attitudes and values.

Among the middle-class groups of both races, working mothers are more likely to have held a higher status position pre-maritally than non-working. This trend persisted after marriage. Thus one reason accounting for the "drop-out" of certain of these women may be their seeming inability to achieve and maintain a high status job. Or it may be that those with a higher status position are simply more motivated to continue working.

Findings do not support the popular theory that working mothers are more likely to have worked prior to marriage than are non-working mothers. Within any given social class and between social classes there are no significant differences in pre-marital employment history.

Study 2: In the interview study, inspection of early analyses indicates that mothers who are employed and those non-employed differ very little in child-rearing philosophies and reported practices with regard to (1) their fostering of dependency or independency in the child, (2) their permissiveness of aggression in the child, (3) the importance they place on achievement by the child, and (4) the nature of sex-typing in their rearing practices. These findings are based on employed and non-employed women carefully matched with respect to variables of social class and family constellation. These findings are consistent with a study carried out at Stanford University, which was planned and coordinated with the study at NIMH, in which controlled observational data were obtained on children's behavior. The two studies investigated similar dimensions in the children's behavior and in the mothers' reports of rearing practices. There were no consistent group differences in the behavior of children of mothers who work and mothers who do not work outside the home.

Scientific Significance: The results of this study contribute to an understanding of the influence of social class and racial membership on the role of the mother in the family. They are also pertinent to contemporary concern with the role of the working mother in family relations and child development. They extend investigation of maternal characteristics to a number of social role variations which may have a bearing on family functioning and the mother-child relationship.

Proposed Course of Project: Analyses will be completed during the coming year. Work has begun on papers for publication.

Part B included Yes [ ] No [x]

Serial No. M-S-D-10
1. Socio-environmental Studies
2. Social Developmental and Family Studies
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Research on the Processes of Internalization of Rules, Standards, and Values

Principal Investigator: Roger V. Burton

Other Investigators: Doris E. Hawkins

Cooperating Units: National Child Research Center, Washington, D. C.; The Town and Country Day School and Camp, Wheaton, Md.

Man Years (Calendar year 1960):		Patient Days (Calendar year 1960):
Total:	1 3/4	
Professional:	3/4	None
Other:	1	

Project Description:

Objectives: To investigate the conditions which dispose four- and five-year-old children to conform to established rules or to yield to the temptation to break rules. Further, to investigate the psychological aftereffects of resistance or yielding, such as guilt, and the association(s) between conformity to established standards and the tendency to experience guilt after a deviation.

Methods Employed: The measure of conformity to established standards (resistance to temptation) is obtained in an experimentally controlled test situation in the child's nursery school.

Study I: This study investigates the influence of the child's need to achieve on his resistance to temptation. Independent measures of level of aspiration, need achievement, and delay of gratification were obtained and correlated with the conformity measure. The psychological effects of the temptation test were obtained by administering a standardized set of incomplete doll stories to each child. Each of these story beginnings portrays a common type of child deviation. The story completions were scored for types of punishment

and for the agent of the action. These scores were considered to be measures of the amount of guilt the child would experience after a deviation of the type portrayed in the story. An experimental group of children were given the achievement measures and the story completions a second time immediately following the temptation test. This design was used to investigate the arousal effects of the temptation test on these measures. A structured interview schedule was used to study the child's cognitions of the temptation test. Teachers rated and ranked the children on personality traits which may be related to the temptation test.

Study II: This study focuses on mother-child interactions. The children are divided into groups of yielders and non-yielders on the basis of their behavior in the temptation test. The child's mother sits with the child during another test, and measures of mother-child interaction are made on dimensions considered relevant to the inculcation of conformity to rules and need to achieve. Different sets of instructions are given to two groups of mothers. One group of mothers is instructed in a manner designed to arouse in them the motive to teach their children conformity to rules. The instructions for the other group are meant to arouse in the mothers the motive to teach the children to want to perform well. A pre-coded questionnaire is given the mothers after the test to control for the differences in the mothers' understanding of the study and for behavior considered by the mother to be different from her regular interaction with the child.

Major Findings: Data collection for Study I is complete, and these data are in the first stages of analysis. The study has shown that the test-retest reliability of the temptation measure is in the high .90's. There are no other findings to report at this time.

Data collection for Study II is about half completed. A pretest indicated that the presence of the mother strongly disposes the child to conform to the established rules even though the mother does not know what they are unless the child tells her. Also, there is the suggestion in the pretest that mothers of children who yield to temptation to break the rules are more directive, interfering, and non-compliant with the child's wishes than the mothers of the non-yielders.

A paper based on a previous experiment in this research project has been submitted to Child Development. The

major findings of this paper, "Antecedents of Resistance to Temptation in Four-Year-Old Children," suggest that direct, physical forms of child-rearing are most efficient in teaching acceptance of standards during the child's early years and that with increasing cognitive development the more symbolic forms of socialization techniques gain in effectiveness. This paper also indicates that resistance to temptation and guilt are not necessarily related and should be studied as distinct phenomena.

Scientific Significance: These studies will contribute to an understanding of the processes involved in the internalization of moral standards. Such information is pertinent to the formulation of a theory of the development of superego behavior and to a general picture of the socialization process.

Proposed Course of Project: These studies are a part of a program of research on the processes of internalization of rules, standards, and values with special emphasis on resistance to temptation and guilt. Findings from previous studies in this program are being prepared for publication. Data analysis of Study I will continue, and data collection of Study II will probably be completed soon.

Future studies will involve additional measures of resistance to temptation, extending the age range of the subjects, and extending the measures of parent-child interaction.

Part B included Yes [ ] No [x]

Serial No. M-S-D-11
1. Socio-environmental Studies
2. Social Developmental and Family Studies
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: A Follow-up Study of Human Aging

Principal Investigator: Marian Radke Yarrow

Other Investigators: Harriet Murphy

Cooperating Units: Laboratory of Clinical Sciences, Laboratory of Psychology, and Social Service Department, NIMH

Man Years (Calendar year 1960):		Patient Days (Calendar year 1960):
Total:	1/4	
Professional:	1/4	120 days
Other:	-	

Project Description:

Objectives: To follow-up the healthy aged men who were studied at NIMH four years ago. To examine stabilities and changes that have occurred with time, and to determine the predictive value of certain physical and psychological indicators present four years ago for current status and functioning.

Methods Employed: Interviews with the aged subject and with a relative of the subject are focused on the subject's present psychological environment and his social functioning: his present attitudes, his goals, his social contacts, the complexity of his daily living, his relationships with his family.

Major Findings: Data collection was begun in October 1960.

Scientific Significance: There have been few studies in which it has been possible to obtain longitudinal data on human aging, particularly intensive biological and behavioral data on the same group of subjects. Data obtained in the follow-up compared with findings of the original study will make it possible to test certain hypotheses concerning the predictive value of given biological and psychological measures, and to formulate additional

hypotheses regarding aging. The follow-up study has value, too, in furnishing a replication of measures, and in so doing permitting assessment of the stability of relationships found in the earlier study.

Proposed Course of Project: Data collection will probably be accomplished during the next year. The subjects are scheduled to come to the Clinical Center in pairs for one to two weeks of study. This spacing will require about nine months in which to see all of the subjects. A report will then be prepared for a scientific journal.

Part B included Yes [ ] No [x]

Serial No. M-S-D-12
1. Socio-environmental Studies
2. Social Developmental and Family Studies
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Household Structure Related to Personality Development

Principal Investigators: Roger V. Burton

Other Investigators: John W. M. Whiting (not NIH)

Cooperating Units: None

Man Years (calendar year 1960):		Patient Days (calendar year 1960):
Total:	1/4	
Professional:	1/4	None
Other:	-	

Project Description:

Objectives: The purpose of this project was to formulate a theory of identification which would account for the findings of previous research. The research of immediate interest to us was cross-cultural studies done using primitive societies. However, we attempted to develop the theory to account for other types of research on identification as well. Testable hypotheses for future studies to be done within our society are suggested. This project is a continuation of work begun prior to the investigator's joining the Laboratory.

Methods Employed: Several cross-cultural studies on primitive societies were integrated. It was seen in this analysis that in some societies certain customs which occur during adolescence were strongly associated with other customs in these societies which occur during infancy and early childhood. These findings are interpreted as showing the direct effect of these early life experiences on the identification process. Studies done in our culture on the lower class and on delinquency were also analyzed. The argument is made that there are significant similarities between the associations found in the cross-cultural studies and the association found between the customs of the lower class and the incidence of delinquency.

Major Findings: Exclusive mother-son relationship during infancy combined with (a) patrilocality, (b) equilocality, and (c) matrilocality are associated with (a) male adolescent initiation ceremony, (b) change of residence at puberty (avunculocality), and (c) couvade, respectively. Sleeping arrangements in which the child does not sleep as close to the mother as the father does, tend strongly to have none of these customs. Research on the lower class and on delinquent groups shows that these subcultures within our society are characterized by similar household and social structure. Also, descriptions of the gang initiation and code of ethics are strikingly similar to the features of primitive initiation rites.

Scientific Significance: This research is relevant to the formulation of a comprehensive theory of socialization with special importance to an understanding of the identification process. It is also specifically related to understanding the social-psychological factors associated with delinquency and other socially undesirable behavior.

Proposed Course of Project: This project was completed during the past year. A paper, "The Absent Father: Effects on the Developing Child," has been finished and accepted for publication by the Merrill Palmer Quarterly.

Part B included: Yes [x] No [ ]

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B: Honors, Awards, and Publications

Publications other than abstracts from this project:

Burton, R. and J. Whiting, "The Absent Father: Effects on the Developing Child," Merrill Palmer Quarterly, Spring issue, 1961.

Honors and Awards relating to this project:

None

Serial No. M-S-D-13

1. Socio-environmental Studies
2. Social Developmental and Family Studies
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Developmental Patterns in the Young Family

Principal Investigators: D. Wells Goodrich, Harold L. Raush

Other Investigators: John D. Campbell, Arden A. Flint, Paul Blank, Walter Sceery.

Cooperating Units: Biosocial Growth Center

Man Years (Calendar year 1960):

Total:	1/4
Professional:	1/4
Other:	-

Patient Days (Calendar year 1960): None

Project Description:

Described in full by Biosocial Growth Center, Project Serial No. MCR(C)12, formerly No. MD(C)4.

Part B included Yes [ ] No [x]

Serial No. M-S-P-1
1. Socio-environmental Studies
2. Community and Population Studies
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: A Comparison of the Social Relationships of Children in the Middle and Lower Socio-economic Strata

Principal Investigators: Melvin L. Kohn and John A. Clausen

Other Investigators: Eleanor Carroll

Cooperating Units: None

Man Years (calendar year 1960):		Patient Days (calendar year 1960):
Total:	2 1/2	None
Professional:	1 3/4	
Other:	3/4	

Project Description:

Objectives: To ascertain whether or not there are consistent and patterned differences in the social relationships of children from the middle and lower socio-economic strata of urban society.

Methods Employed: Structured interviews with a sample of middle and lower socio-economic status parents of 9-10 year old children, together with interviews with a sub-sample of the children themselves. The interview schedule for parents was designed to illumine the several dimensions of the parent-child relationships, the values of the parents most relevant to their behavior as parents, their evaluations of their children's behavior, and their knowledge and structuring of their children's relations with other children. The interview schedule for the children has been designed to elicit their perceptions of their relations with their parents, as well as a more complete picture of their relationships with other children.

Major Findings: Most theories of personality development have been based on the model of a family in which mother's and father's intra-familial roles are necessarily differentiated, with mother specializing in providing emotional

support and father in imposing constraint. However useful a first approximation this may be, both middle- and working-class variations on this general theme are sufficiently great to compel a more precise formulation.

Our data are at least partly consistent with the mother-supportive, father-constraining formulation, for even in middle-class families almost no one believes that the child turns to father more readily than to mother. Yet, in a sizeable proportion of middle-class families it is mother who takes primary responsibility for imposing constraints on sons, and father is at least as supportive as mother. And although middle-class fathers seldom seem to be as supportive of daughters as are their wives, it cannot be said that fathers typically specialize in constraint even with daughters. In most middle-class families, mother's and father's roles do not seem to be sharply differentiated. To the degree that they are, a new division of responsibilities is developing, with each parent taking special responsibility for support of children of his own sex.

Mother's and father's roles are more sharply differentiated in working-class families, with the children almost always feeling that mother is the more supportive parent. Yet, despite the high valuation put on the constraining function, fathers do not necessarily specialize in setting limits for the children, even for the sons. In some working-class families mother specializes in support, father in constraint; in others--perhaps in most--the division of responsibilities is that mother raises the children, father provides the wherewithal. This pattern of role-allocation probably is and has been far more prevalent in American society than the formal theories of personality development have recognized.

Scientific Significance: One plausible interpretation of the disproportionately high rates of schizophrenia in the lower socio-economic strata is that the childhood social experiences of persons from these strata have predisposed them to illness. Though plausible, this interpretation does not get us very far in our understanding of schizophrenic personality development until we are able to specify in detail the respects in which the childhood social relations of these persons differ from those of other groups in the society. This knowledge we seek to secure in the present research. We hope that the results of the study will make possible the formulation of more

penetrating hypotheses about the role of social experience in the development of schizophrenia than those that have been produced to date.

Proposed Course of Project: The major analyses originally contemplated when this project was designed have now been completed. We may, however, utilize the data further to pursue problems which have emerged in the course of the data-analysis, e.g., the reasons for the apparently different ways in which middle- and working-class parents ascribe sex-typed roles to their children, the possible relationship between family structure and the child's peer-group activities.

Part B included Yes [x] No [ ]

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B: Honors, Awards, and Publications

Publications other than abstracts from this project:

Kohn, Melvin L. and Eleanor E. Carroll, "Social Class and the Allocation of Parental Responsibilities," Sociometry, Vol. 23, December, 1960.

Clausen, John A. and Melvin L. Kohn, "Social Relations and Schizophrenia: A Research Report and a Perspective," in The Etiology of Schizophrenia, Don D. Jackson, M.D., Editor, Basic Books, Inc., New York, 1960.

Honors and Awards relating to this project:

None

Serial No. M-S-P-3
1. Socio-environmental Studies
2. Community and Population Studies
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Pre-hospital Social Factors, Treatment with the Tranquilizing Drugs and Behavior as Prognosticators of Successful Release from a Mental Hospital

Principal Investigator: Erwin L. Linn

Other Investigators: None

Cooperating Units: Saint Elizabeths Hospital

Man Years (calendar year 1960):		Patient Days (calendar year 1960):
Total:	--	
Professional:	--	None
Other:	--	

Project Description:

The principal investigator on this project left the Institute in January of 1960. Before leaving the Institute, he had published three articles, which answered the primary questions for which the project had been designed.

Serial No. M-S-P-4
1. Socio-environmental Studies
2. Community and Population Studies
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: A Twin Family Study of Mental Deficiency

Principal Investigators: Gordon Allen and Franz J. Kallmann (non-PHS)

Other Investigators: None

Cooperating Units: New York State Psychiatric Institute

Man Years (calendar year 1960):		Patient Days (calendar year 1960):
Total:	-	None
Professional:	-	
Other:	-	

Project Description:

The principal investigator transferred to the Office of the Chief during the year. For a full description of this project see Serial No. M-S-C-5.

Serial No. M-S-P-6
1. Socio-environmental Studies
2. Community and Population Studies
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Jobs and Health: An Evaluation of the Meaning of Work and Its Relation to Health

Principal Investigator: Stephen T. Boggs

Other Investigators: None

Cooperating Units: None

Man Years (Calendar year 1960):		Patient Days (Calendar year 1960):
Total:	1 1/2	
Professional:	1	None
Other:	1/2	

Project Description:

Objectives: The purpose of this study is to specify some of the ways in which the personal meaning of a man's job and work career are related to his emotional and physical health. We have assumed that stress results when key values in the job and career are threatened. Accordingly, we are investigating the relationship between (1) social values pursued in work, (2) various features of the job, (3) career prospects, and (4) manifest emotional and physical disturbance.

Methods Employed: The study has been focused upon the men working as research assistants and technicians in the laboratories at NIH. Two hundred of these men, all over 30 years of age and who do not hold the Ph.D. degree, were asked to cooperate in the study. Generously, 184 of them filled out a structured, written questionnaire; and 150 also were interviewed.

To analyze the meaning which their jobs have for them, we asked the men what they hope to achieve through their jobs, what they thought of various features of their jobs, and what prospects they saw for advancement within the occupation or outside it.

Emotional reactions were assessed from questions about feelings pertaining to the job, preoccupation with it, and self-reports of health and physical symptoms. Physical condition has been estimated from reports of conditions diagnosed.

Major Findings: About half of the men regard opportunity for advancement as the most important thing about their jobs. Such men have demonstrably different attitudes towards promotion, further education, and changes in the work they perform. Generally, it seems that this emphasis upon advancement increases when men are not promoted after a longer time at NIH, rather than decreasing, as we anticipated. Men who do not emphasize advancement more often desire to leave the occupation entirely, thus suggesting that something of value is given up when advancement is not of primary importance on the job.

Other values, such as security, or interest in the work itself, vary with social class background. Emphasis upon them does not seem to change markedly as a result of experience on the job.

Scientific Significance: In American culture the job and work career seem to contribute much to a man's view of himself. Findings from this study may add to our knowledge of how occupational goals and work values affect emotional reactions to the job. They can thus help to clarify the relationship between job satisfaction and emotional stress, about which there has been much speculation, and provide systematic evidence for comparative studies of the mental health of workers in other occupations.

Proposed Course of Project: The next step will be to see whether emotional reactions and physical condition vary among men with different value-orientations when such things as the nature of the work, relations with the investigator, and career prospects vary. It is hoped that the first findings from the study can be published during the coming year.

Part B included: Yes [ ] No [x]

Serial No. M-S-P-7
1. Socio-environmental Studies
2. Community and Population Studies
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Zygosity Diagnosis in Triplets and Quadruplets

Principal Investigator: Gordon Allen

Other Investigators: None

Cooperating Units:
1. Laboratory of Psychology
2. Adult Psychiatry Branch
3. Laboratory of Blood and Blood Products
4. National Office of Vital Statistics

Man Years (calendar year 1960):		Patient Days (calendar year 1960):
Total:	-	None
Professional:	-	
Other:	-	

Project Description:

The principal investigator transferred to the Office of the Chief during the year. For a full description of this project see Serial No. M-S-C-6.

Serial No. M-S-P-8
1. Socio-environmental Studies
2. Community and Population Studies
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Development of Self-Images and Self-Ideals in Normal Adolescence

Principal Investigator: Morris Rosenberg

Other Investigators: None

Cooperating Units: None

Man Years (calendar year 1960):		Patient Days (calendar year 1960):
Total:	3	None
Professional:	2/3	
Other:	2 1/3	

Project Description:

Objectives: (a) To study the content and evaluation of self-image and the nature of self-ideals in adolescence; (b) To study the various elements which constitute the structure of the self-image, such as self-evaluation, stability of self, salience of self, certainty of self-estimates, and content of the self, and to examine the relationship among these elements; (c) To study the relationship of self-esteem to other indicators of emotional disturbance, such as tension, depression, and anxiety, as well as to their manifestations in the form of psychosomatic symptoms; (d) To learn about self-values and self-estimates among people varying in certain demographic characteristics; (e) To examine the association between academic history and self-esteem; (f) To examine the association between early relationships with peers and with siblings and self-esteem; (g) To investigate the relationships between authority patterns in the family and certain aspects of child-rearing to subsequent self-conceptions; (h) To examine the significance of group integration for self-acceptance; (i) To investigate the relationship of attitudes toward the self and attitudes toward others; (j) To examine the

relationship between self-esteem and a selected group of socially significant attitudes and behavior, such as position in peer groups, participation in peer activities, occupational aspirations and values, and feelings of social responsibility.

Methods Employed: The structured questionnaire is the major instrument employed in this study. Three separate but overlapping questionnaires have been administered to a sample of high school juniors and seniors. Ten high schools in New York State, stratified by size of community and chosen by a random procedure, participated in the study. These self-administered questionnaires, which were anonymous, were filled out by 5,077 high school students. The data have now been coded, punched onto IBM cards, and verified, several Guttman scales have been constructed, and other steps have been taken to prepare the data for analysis. It has proved possible to begin the analysis of certain questionnaire forms while others are still being processed.

Major Findings: The data analysis is not yet sufficiently far advanced to make firm statements of results at this time.

Scientific Significance: Recent research in psychology and psychoanalysis has focussed increasingly upon the self as an important factor in personality. The social and cultural determinants of self-image, however, have not been adequately investigated. The study of the self and self-esteem is relevant to the understanding of personality processes, and may have an important bearing upon certain symptoms of psychological problems, such as tension, depression, and anxiety.

Proposed Course of Project: The coming year will be devoted to an intensive analysis of the data collected by these questionnaires. Plans are under way to supplement the quantitative data obtained by the structured questionnaires with qualitative data obtained by means of a small number of intensive interviews with adolescents.

Part B included Yes [ ] No [x]

Serial No. M-S-C-2
1. Socio-environmental Studies
2. Office of the Chief
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: The Impact of Mental Illness Upon the Family

Principal Investigator: John A. Clausen

Other Investigators: Harriet S. Murphy and Eleanor Carroll

Cooperating Units: Saint Elizabeths Hospital, Washington, D. C., Springfield State Hospital, Sykesville, Maryland, and Spring Grove State Hospital, Catonsville, Maryland

Man Years (calendar year 1960):		Patient Days (calendar year 1960):
Total:	1 1/2	None
Professional:	3/4	
Other:	3/4	

Project Description:

Objectives: To study the effects upon the family of the father's or mother's "functional" mental illness, by focusing on a limited number of hypotheses and questions raised by an earlier study, within the following areas: (1) the effects of mental illness upon the personal relationships within the family and the family organization, (2) the family's understanding and perspectives of the illness, and (3) the social implications of the illness.

Methods Employed: The data are obtained through two structured interviews scheduled shortly after the patient's admission to the hospital and a third interview after several months of hospitalization. The respondents are spouses of schizophrenic patients who are first admissions to the mental hospital.

Major Findings: There are no new findings to be reported this year.

Scientific Significance: This study provides data relating to needs in public education regarding mental illness, to the kinds of help needed by the families of patients and

to the kinds of social and psychological problems for patient and family attendant to hospitalization of a mental patient.

Proposed Course of Project: Data collection was completed during 1960 and considerable effort was devoted to the abstraction of materials from hospital records and the codification of both the data secured in our interviews and those secured from the hospital records. The principal investigator left the Institute in early September. He proposes to continue data analysis at the University of California.

Part B included Yes [ ] No [x]

Serial No. M-S-C-3
1. Socio-environmental Studies
2. Office of the Chief
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: The Adaptation of the Mental Patient to his Family Upon Return from Hospitalization

Principal Investigator: John A. Clausen

Other Investigators: Harriet S. Murphy, Eleanor Carroll and Carmi Schooler

Cooperating Units: Saint Elizabeths Hospital, Washington, D. C., Springfield State Hospital, Sykesville, Maryland, and Spring Grove State Hospital, Catonsville, Maryland

Man Years (calendar year 1960):		Patient Days (calendar year 1960):
Total:	$1\frac{1}{4}$	None
Professional:	$\frac{1}{2}$	
Other:	3/4	

Project Description:

Objectives: To study the rehabilitation process following the patient's discharge from a mental hospital, in terms of two interdependent sets of dimensions: (a) the patient's progress toward mental health, and (b) the changing structure and functioning of the family of the patient.

Methods Employed: Patients and families are the same as those studied in project M-S-C-2 and certain of the data secured for that project will be basic to the present project. Data are obtained through interviews with the patient and the patient's spouse and with selected significant others in the patient's social environment. The period of follow-up varies, though for all patients there will be assessments or status reports as of one month, six months and one year after leaving the hospital. Some patients studied in the early phase of data collection will have three to four years of follow-up; patients obtained in the late phase will have one year of follow-up.

Additional data come from hospital case reports, psychiatric evaluations of patient's condition at discharge and the investigator's observational ratings of family and patient.

Major Findings: No new analysis has been undertaken. During the past year, follow-up interviews have been conducted with the families of former patients, at the scheduled intervals following hospital discharge.

Scientific Significance: The high readmission rate of patients to mental hospitals points to the need for research into the factors influencing the discharged patient's adjustment to the family and the community. The present study will add knowledge concerning the kinds of stresses and problems encountered in the process of rehabilitation, and the relationships between conditions in the patient-family-community situation and successful and unsuccessful rehabilitation.

Proposed Course of Project: Data collection was completed during 1960 and considerable effort was devoted to the abstraction of materials from hospital records and the codification of both the data secured in our interviews and those secured from the hospital records. The principal investigator left the Institute in early September. He proposes to continue data analysis at the University of California.

Part B included Yes [ ] No [x]

Serial No. M-S-C-4
1. Socio-environmental Studies
2. Office of the Chief
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Factors Relating to the Differential Attribution of Authority

Principal Investigator: Melvin Ember

Other Investigators: None

Cooperating Units: Final arrangements not made as yet.

Man Years (calendar year 1960):		Patient Days (calendar year 1960):
Total:	1	None
Professional:	1	
Other:	-	

Project Description:

Objectives: To investigate some factors which may relate to how members of an organization differentially attribute authority, i.e., legitimate power, to each other.

Methods Employed: The design of the present study is modeled after that of an earlier, anthropological field study (done by the principal investigator) of differential political change in three villages of American Samoa. In that earlier study, the general problem was to explain the differences in the amount of authority attributed to the council of chiefs in the three villages. In the present study, however, the general problem is to explain the differences in the amount of authority attributed to individuals of the same formal status in the same type of organization.

The social units to be compared in the present study will be nursing units in a mental hospital. Three such units will be studied, just as three villages were studied in Samoa. Each nursing unit studied will be identified as the jurisdiction of a given head nurse and each will include the nursing staffs of at least two wards. This

latter requirement is specified so that it will be possible to compare at least two occupants of a given position in the formal table of organization (excepting, of course, the position at the top of the structure--that of the head nurse). The three units of study will be selected on the basis of evidence, to be collected in a preliminary survey of the hospital "culture," which points to differences between the units with regard to how much the members of each accept the formal authority structure. (Selection of the three villages studied in Samoa was made in the same way.) Following selection of the units, observations and interviewing will be conducted on one of the units. During this phase of the research, the investigator plans to spend all of his time on that unit in order to find out what kinds of activities are organized in such a nursing unit, how often they are organized, and how they are organized (i.e., who initiates and who executes them). Once the details of organizational behavior in the first nursing unit is known, quantitative measures of the amount of authority accorded by each member of the unit to the others will be developed. The data for these measures will then be collected by interview. As part of the same interview, each member of the unit will be questioned as to the factors which are hypothesized to relate to how he attributes authority to his co-workers. (One example of such a factor is whether or not the head nurse treats the occupants of the same status equally. Another factor to be investigated is the degree of correspondence between expectations as to the responsibilities of a particular person and the actual behavior of that person relevant to those expectations.) Following the completion of this first phase of the study, i.e., the collection of data for the first nursing unit to be studied, the same kinds of data will be collected for the other two units to be studied.

Major Findings: None as yet. The study will be initiated as soon as final arrangements permit.

Scientific Significance: We have a good deal of evidence as to the social and cultural conditions which lead to the decay of authority as it is attributed to groups, such as village councils in Samoa. What we do not have is evidence bearing on the interactional and psychological mechanisms by which that process is effected. That is, we still do not know why a member of an organization will begin to stop feeling obligated to go along with the attempts by the customary authority figure to initiate

behavior for him. The present research is designed to provide some information which may permit us to resolve this problem, on the assumption that we can make processual inferences from correlational data. What we seek, in sum, is evidence of the interpersonal processes which underlie the cultural change which is the decay of authority.

Proposed Course of Project: When final arrangements are made with the cooperating hospital, the next step will be to informally seek the kind of information on the basis of which the three nursing units for study will be selected. At this time it is only possible to guess the form that information will take, but it is anticipated that it will be obtained from either informal observation on the wards or from administrative personnel. After the required information is secured and the three units selected for study, collection of data will proceed as described above.

Page B included Yes [ ] No [x]

Serial No. M-S-C-5
1. Socio-environmental Studies
2. Office of the Chief
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: A Twin Family Study of Mental Deficiency

Principal Investigator(s): Gordon Allen and Franz J. Kallmann (non-PHS)

Other Investigators: None

Cooperating Units: New York State Psychiatric Institute

Man Years (calendar year 1960):		Patient Days (calendar year 1960):
Total:	7/8	
Professional:	3/4	None
Other:	1/8	

Project Description:

Objectives: To assess the role of environmental factors in mental deficiency of different types. Also to develop better methods for the collection and interpretation of twin data in medical research.

Methods Employed: A reporting system set up in 1937 by Dr. Kallmann provided index information on a large number of mentally subnormal twins in New York State, mainly in the State schools for Mental Defectives. During the four year period, July 1952 to June 1956, additional information was abstracted from institutional records and obtained on visits to homes and hospitals. Accessible twins were examined, many of them with the aid of X-rays, electroencephalograms, and psychological tests.

Pairs studied in detail were classified as to zygosity. Clinical diagnoses were reviewed in the light of all information obtained. Case studies are summarized and essential information is punched on McBee cards in preparation for statistical analysis.

Patient material: The sample consists of 570 multiple births represented by 715 index cases. One hundred and seventy-eight pairs have been studied in detail.

Major Findings: Complex statistical biases in the detection and accessibility of mentally defective twins make absolute concordance rates for the sample difficult to interpret. However, relative concordance rates for two major diagnostic classes, excluding mongolism, present a striking contrast between monozygotic and dizygotic twins, even when opposite sex dizygotic sets are kept separate. In Table 2, the difference between the two types of dizygotic twins is not significant (chi-square 2.57), but that between MZ and same-sex DZ sets is highly significant (Chi-square 10.81).

Table 1. Twin pairs with high-grade, undifferentiated defect

	MZ	DZ (same-sex)	DZ (opposite-sex)
Concordant	16	14	11
Discordant	0	4	4

Table 2. Twin pairs with low-grade or clinical mental defect

	MZ	DZ (same-sex)	DZ (opposite-sex)
Concordant	24	12	5
Discordant	10	24	30

Scientific Significance: In the second table above, which represents the more severe types of mental defect, with evident congenital or neonatal pathology, the predominance of MZ pairs among the concordant, and of DZ pairs among the discordant, strongly suggests that genetic factors play an important role. On the other hand, the ten pairs of MZ twins discordant for clinical defects show the action of environmental factors. Detailed review and comparison of these classes may provide some new leads for the separation of genetic and non-genetic etiologies in organic mental defect.

Proposed Course of Project: Analysis of data should be completed in 1961, and publications should be prepared during the year.

Part B included: Yes [ ] No [x]

Serial No. M-S-C-6
1. Socio-environmental Studies
2. Office of the Chief
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Zygosity Diagnosis in Triplets and Quadruplets

Principal Investigator: Gordon Allen

Other Investigators: Joseph Schachter, Chief, Natality Analysis Branch, National Office of Vital Statistics

Cooperating Units: (1) Laboratory of Psychology
(This project was originally conceived as part of, and carried out in cooperation with, Project M-P-C(C)-12.)
(2) Adult Psychiatry Branch
(3) Laboratory of Blood and Blood Products
(4) National Office of Vital Statistics

Man Years (calendar year 1960):		Patient Days (calendar year 1960):
Total:	3/8	
Professional:	1/4	None
Other:	1/8	

Project Description:

Objectives: To determine the zygosity of quadruplets and triplets studied in the Adult Psychiatry Branch; to gather statistics and develop methods that will facilitate such diagnoses in future; and to devise a statistical method for describing the phenotypic variation in plural births.

Methods Employed: For the purposes of this study, and as one of the objectives, the classical "similarity method" has been modified to yield probability statements. This requires, among other things, knowledge of the empirical probabilities of different types of plural births, and to this end unpublished data of the National Office of Vital Statistics are being analyzed by manual and machine methods. Also, the laws describing variation in sets of plural births are partly unknown, and a computer program will be developed to provide statistical models of populations of plural births.

Patient material: One set of triplets and one set of quadruplets were used in this study while they were on the adult psychiatry wards for clinical investigation.

Major Findings: For a set of twins there are only two possible hypotheses about zygotic origin. For triplets there are five and for quadruplets, fifteen. Some of the triplet and quadruplet hypotheses cannot be differentiated on the basis of simple genetic traits like blood groups and quantitative differences must be brought into the calculations. This can apparently be done by combination of individual probabilities for separate pair differences within the set. A likely formula has been found for combining the probabilities, but it still lacks theoretical and empirical validation.

Twinning rates are found to vary widely over different years and different sections of the country, even after race and maternal age are taken into account. Analysis of birth-order effects, now under way, should show whether the residual variation is mainly due to birth order or to socio-economic status, neither of which has hitherto been thoroughly documented.

Scientific Significance: Frequencies of plural births of all types are functions of maternal ovarian physiology and of early embryonic processes. Knowledge of these relative frequencies, especially in relation to maternal age and birth order, may therefore afford new insight into mechanisms controlling ovulation and early embryonic development.

A precise quantitative method for evaluating the probability that a set of triplets or higher multiple births belongs to a particular type makes more feasible the use of such subjects in exacting research. One problem that may thus be opened to attack is the assessment of variation between individuals in stability of traits subject to some degree of environmental modification.

Proposed Course of Project: With each analysis of data new phenomena present themselves for investigation, and the study will probably continue on a part time basis through 1961 and beyond.

Part B included: Yes [x] No [ ]

PHS-NIH
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Calendar Year 1960

Part B: Honors, Awards, and Publications

Publications other than abstracts from this project:

Allen, G., "A differential method for estimation of type frequencies in triplets and quadruplets," American Journal of Human Genetics, Vol. 12, 1960, pages 210-224.

Allen, G., "The M quadruplets: I. Probability of uniovular origin judged from qualitative traits," Acta Geneticae, Medicae et Gemellologiae, Vol. 9, 1960, pages 240-254.

Allen, G., "The M quadruplets: II. The interpretation of quantitative differences," Acta Geneticae, Medicae et Gemellologiae, Vol. 9, 1960.

Honors and Awards relating to this project:

None

Serial No. M-NB-1
1. Lab. of Neurobiology
2.
3. Bethesda, Maryland
4. Continuation of:
NIMH-NP-BS-1 (1959)
NINDB-NC-13 (1958)

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Vestibular Influences on Spinal Mechanisms

Principal Investigator: Bo E. Gernandt, M.D.

Other Investigators: Sid Gilman, M.D., David Megirian, Ph.D., Muneo Shimamura, M.D., and Robert B. Livingston, M.D.

Cooperating Unit: None

Man Years
Total: 2.5
Professional: 2.3
Other: .2

Project Description:

Objectives: Our recognition of the spatial world in which we live and of our own bodies disposed within that space is derived from several channels of sensory information: visual, vestibular, proprioceptive, and visceral. These systems are involved in most of our perceptual, experiential, and motor activities. Proprioceptive and vestibular systems are interdependent in controlling posture and locomotion; streams of afferent impulses generated by receptors in each of these systems interact in supraspinal and spinal nervous structures and converge to influence the activity of the final common path, the motor units. The sensory organ of particular importance to the maintenance of equilibrium and orientation is the nonauditory, phylogenetically oldest portion of the inner ear, the labyrinth or vestibular apparatus. The objectives of the present investigations are to analyze the complex mutual interactions among activities mediated through the vestibular, segmental and intersegmental propriospinal, and pyramidal systems, as reflected by alterations in spinal motor outflow.

Ascending and descending propriospinal neurons, long and short, interconnect the spinal segments and enable the cord to function integratively. The significance of the descending system in the transmission of reflex activity has been previously described. The present experiments are designed to reveal the physiological properties of ascending propriospinal activity as it traverses different distances along the neuraxis. Manifestation of an ascending intersegmental tonic influence upon reflex activity has long been recognized in the Schiff-Sherrington phenomenon. However, only two pieces of electrophysiological evidence suggesting long ascending propriospinal conduction capable of evoking reflex activity have been found in the literature and both observations were incidental to other pursuits.

Methods employed: The method of Gernandt and Andersson for stimulation of the vestibular nerves in cats is employed. Responses are recorded from a variety of spinal nerves, ventral roots, and small filaments of the ventral roots. Additional input stimulation is applied to the cerebellum, cerebral motor cortex, and to various peripheral nerves and dorsal roots.

Major findings: i) The motor outflow in response to vestibular stimulation shows significant differences when recorded from consecutively lower levels of the spinal cord. The progressive decline and disappearance of the earliest component of the response is presumed to reflect attenuation of the vestibulospinal connections along the caudal extent of the neuraxis. Vestibular responses at lumbosacral levels reflect activity mediated predominantly via reticulospinal pathways or their functional continuations as propriospinal intersegmental relays. Interactions are analyzed and a comparison is made of the influences upon lumbosacral motor pools by activation of the vestibular, segmental, and intersegmental propriospinal relay systems.

The importance of tonic and phasic suprasegmental control of spinal reflex activity is investigated. In decerebrate preparations, single shock activation of the descending vestibular or propriospinal mediating systems evokes a pattern of facilitatory and inhibitory excitability changes of lumbosacral ventral horn cells. The prominent inhibitory influence of intersegmental propriospinal activity can be eliminated by high spinal transection. The protracted inhibition of local and long spinal reflex activities following high-frequency vestibular or brachial plexus stimulation is abolished by a small localized incision in the midline at the caudal limit of the medulla, interrupting continuity between medial reticular formation and spinal segments.

ii) The effects of interaction between vestibular, pyramidal, and cortically evoked extrapyramidal activities, as reflected by recordings from brain stem reticular formation and motoneurons of cervicothoracic and lumbosacral levels, have been studied in cats. The significant size of the spinal motoneuron responses to motor cortex stimulation remaining after low medullary pyramidotomy demonstrates the important contribution of impulses conducted in extrapyramidal channels relative to those mediated through pyramidal pathways. Activity transmitted in the most rapidly conducting pyramidal fibers arrives at cervicothoracic levels in advance of impulses conveyed extrapyramidally, but there is hardly any temporal separation of the volleys by the time they reach lumbosacral levels. Following pyramidotomy interactions between vestibular, cortically evoked "pure" extrapyramidal, and "pure" pyramidal activity elicited by stimulation of the medullary pyramid below the site of transection, have been analyzed.

Responses to motor cortex stimulation recorded from the brain stem reticular formation are markedly diminished by conditioning vestibular volleys, but interference with vestibular responses at the same recording site by preceding cortical shocks is weak. In the competition for access to the final common path, particularly at cervicothoracic levels, vestibular evoked activity dominates and the vestibular pattern of discharge is preserved or even supplemented at the expense of cortically evoked activity. A component of the response to vestibular stimulation is selectively exalted by conditioning pyramidal or extrapyramidal stimulation.

The monosynaptic component of a lumbosacral segmental reflex response is markedly exalted during simultaneous high frequency motor cortex stimulation but suffers a protracted post-stimulatory inhibition. Pure extrapyramidal activation by high frequency motor cortex stimulation after pyramidotomy results in an initially strong but gradually weakening facilitation of the test reflex and a more rapid and profound post-stimulatory inhibition. Selective pyramidal stimulation gives rise to a marked enhancement of the segmental reflex activity which endures for some minutes post-stimulatory. The significance of the brain stem as a source of the post-stimulatory inhibition is discussed in the light of the present and previous studies.

iii) Influences on spinal motor pool excitability by activity evoked in ascending propriospinal neurons are weak or absent depending upon the number of interposed segments between the sites of afferent stimulation and reflex response

recording, whereas those of the descending system are extensive and powerful. Elicitation of a reflex response at the cervico-thoracic levels by activation of ascending propriospinal pathways at lumbosacral levels requires exaltation by strychnine. Conduction velocities along the ascending and descending propriospinal trajectories are uniform throughout their length, although the ascending pathways are substantially slower.

Significance to Science: The mechanisms underlying muscle tone, posture, and locomotion are basic neurophysiological problems. Any increased knowledge of mechanisms of circuitry in the central nervous system and especially of integration between the classical and the diffusely projecting systems is of especial value.

Proposed Course of Project: It is proposed to pursue a continuing stepwise analysis of the mechanisms of vestibular integration.

Part B included: Yes

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Part B - Publications;

Gernandt, B. E., and Gilman, Sid. Vestibular and propriospinal interactions and protracted spinal inhibition by brain stem activation. J. Neurophysiol., 1960, 23: 269-287.

Gernandt, B. E., and Gilman, Sid. Interactions between vestibular, pyramidal, and cortically evoked extra-pyramidal activities. J. Neurophysiol., 1960, 23: 516-533.

Serial No. M-NB-2
1. Lab. of Neurobiology
2.
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Mathematical Study of Problems of Visual Perception

Investigator: Rosalind B. Marimont

Cooperating Unit: Mathematical Research, OADR-NIAMD

Man Years: Total: Approximately 1/6 5 months part time at approximately 40 percent of full time.

Project Description:

Objectives: To study problems of visual perception, in particular color vision and pattern recognition from the viewpoint of mathematics, physics and the logical design of electronic computers which attempt to duplicate some of these functions. The problem now being studied is that of color vision, which has been described as a happy hunting ground for theorists, in that most of the fundamental questions are still unanswered. Apparently different theories are necessary to explain various phenomena. There are, however, certain basic experimental findings, embodied in the fundamental laws of color vision, which must be logical consequences of any valid theory. While most proposed theories contain assumptions to ensure compliance with these laws, the question of necessary conditions has apparently not been completely solved, i.e. the sufficient assumptions may be overly restrictive.

Recent experimental results show that these fundamental laws hold only approximately, so that certain relaxations of the necessary and sufficient conditions are required to explain the observed behavior. An attempt will be made to determine the formal and mathematical nature of these corrections, and to seek physical structures that might account for them. To sum up, these objectives may be listed for the study of color vision.

1. Mathematical treatment of the laws of color vision, including derivation of the necessary and sufficient conditions required by them.

2. Study of experimental results to ascertain the nature and extent of deviations from these laws.

3. Mathematical treatment of the deviations, and search for physical elements that account for them.

Major findings: Grassman's set of three laws and Abney's law have been found to be expressions of a property which may be described as quasi-additivity. This property asserts that if we have 4 lights, L_1, L_2, L_3, and L_4, and if L_1 matches L_2, and L_3 matches L_4, then the sum (mixture) of L_1 and L_3 will match the sum of L_2 and L_4. If by "match" we mean appear identical in all attributes, i.e. hue, saturation, and brightness, then the above statement implies all of Grassman's laws. If we use "match" to mean match in brightness alone, then Abney's law is stated.

The aid of Dr. Norman Shapiro has been enlisted for the first of the above objectives. Preliminary results on Abney's law indicate that brightness must be expressible as a one-to-one function of a linear operator. The conventional model of one or more visual pigments with fixed spectral absorption characteristics, independent of the nature of the light impinging, and with the generated nerve impulse either a logarithmic or power function of the intensity of incident light is an example of such a system. The more general problem of Grassman's laws is now being studied.

Recent experimental evidence shows that there are significant deviations from both these laws. Russian studies of Abney's law show large discrepancies in the short wave region of the spectrum. Other studies indicate deviations everywhere, if the method of brightness matching is used, but good agreement if flicker methods are used. These results will require careful study.

On the third phase, i.e. physical structures which might account for the discrepancies, the configuration of the outer limbs of the photoreceptors suggests itself to the physicist as a possible source of unexpected effects. The small diameter of these structures--only about 2 or 3 wavelengths indicates that light would be propagated by means of wave guide modes of transmission rather than by straight lines. Experimental and theoretical studies of

propagation in glass fibers of similar diameter show also a rather surprising coupling between adjacent fibers. The laminated structure of the limbs might also have some frequency selective effect. Whether these effects are major or minor cannot be determined until the quantitative relationships are explored.

Proposed course: Direction of future work is indicated in the discussion of findings, and may be summarized as further pursuit of the three objectives listed above.

Part B included: No

Serial No. M-NB-3
1. Lab. of Neurobiology
2.
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Mechanisms Underlying Enduring Effects of Prolonged Sensory Stimuli

Principal Investigator: Robert B. Livingston, M.D.

Other Investigators: Arnold Starr, M.D.

Cooperating Unit: None

Man Years
Total: 1.2
Professional: .8
Other: .4

Project Description:

Objectives: Enduring effects of prolonged sensory stimuli are commonplace observations. Thus, unsteadiness and motion of the environment may persist for several days following a sea voyage. Noise "in the head" occurs following exposure to loud noises. Similar observations are noted following prolonged cutaneous stimuli. The object of this study is to determine what are the alterations induced in the sense organs and in the central nervous system as a result of prolonged sensory stimulation and to define the structures and conditions essential for these phenomena. We believe such experiments may provide a means for examining mechanisms relating to learning and memory.

Methods: Animals with chronically implanted electrodes in the primary relay and sensory association nuclei are subjected to initiating stimuli for varying periods of time. The electrical activity of these areas are measured by means of a response integrator for changes in background of neural activity before, during, and following stimulation. The effects of drugs, anesthetics, and ablations of neural structures upon this activity are to be recorded and analyzed.

Results: Six months have been spent preparing equipment and developing techniques. A few animals have been prepared with electrodes implanted along the auditory and vestibular sensory paths. These animals are now beginning to be tested.

Significance: The characteristics of the nervous system which account for enduring functional changes following prolonged sensory stimulation may be related to persisting sensations such as phantom limb sensation, intractable pain, and various sensory hallucinations and delusions. Knowledge of the mechanisms underlying enduring functional changes may be of assistance toward understanding several kinds of clinical problems as well as fundamental mechanisms which possibly relate to learning and memory.

Course: Continuation of these and related experiments.

Part B included: No

Serial No. M-NB-4
1. Lab. of Neurobiology
2.
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Modification of Activity in Sensory and Non-sensory Corticipetal Pathways

Principal Investigator: Robert B. Livingston, M.D.

Other Investigators: Gabriel P. Frommer, M.S.

Cooperating Unit: None

Man Years
Total: .7
Professional: .45
Other: .25

Project Description:

Objectives: Recent experimental work has demonstrated that activity in sensory pathways may be modified by stimulation of the mesencephalic reticular formation, portions of the cerebral cortex and cerebellum, among other sites. Further, activity in sensory pathways has been shown to be functionally modified according to the state of EEG and behavioral arousal. While there is general agreement on the existence of such changes, the nature, function, and quantitative and qualitative properties of this phenomenon are controversial. The objectives of the present investigation are to try to further comprehend this phenomenon and to determine whether similar changes can be effected in a parallel, primarily non-sensory circuit.

Methods: The trigeminal somatosensory pathway and the somatomotor pathway from the cerebellar dentate nucleus, both projecting to the sensorimotor cortex by way of the thalamus, will be used in this experiment. Test stimuli will be applied to the trigeminal nucleus or its peripheral projection and to the dentate nucleus of the parallel non-sensory system. Conditioning stimuli will be applied to a variety of central

nervous system structures. Experiments will be initiated on deeply anesthetized cats to test the basic pathways. Thereafter, we will attempt to establish whatever may be the degrees of plasticity of these systems as tested on cats with chronically implanted electrodes in a variety of neurophysiologically and behaviorally controlled situations.

Major Findings: Progress to date includes only preliminary equipment development.

Significance to Science: The discovery that the classical sensory systems do not act as simple and reliable transmission lines from periphery to cortex represents a major modification in notions of the neural basis of perception. Further investigation of central nervous system control over activity in sensory pathways will yield direct evidence on these systems in the normally functioning waking organism and provide a more valid neurophysiological basis for behavioral phenomena relating to sensation and sensory experience.

Part B included: No

Serial No. M-D(C) 1

1. Clinical Investigations
2. Office of the Director
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1959

Part A.

Project Title: The Analysis of the Psychotherapeutic Process, Particularly the Psychoanalytic Process

Principal Investigator: Robert A. Cohen

Other Investigators: David Shakow, Allen Dittmann, Morris Parloff, Paul Bergman, Mabel Cohen, and Edith Weigert

Cooperating Units: Laboratory of Psychology

Man Years: 0.25

Project Description:

Objective: To conduct an intensive study of the psychoanalytic process.

Methods Employed:

1. Data Collection: Naturalistic recording by motion pictures and stereophonic sound of portions and of psychoanalytic (and in some cases of other psychotherapeutic treatments of adults and children with a variety of emotional disorders. Sound recordings are made of weekly discussions between the therapist and an experienced consultant, during which the former presents a review of the therapeutic transactions of the week, including his conceptions of the nature of the developing therapeutic relationship and of the strategy underlying his interventions. These recordings will not be made available to the data analysts until they have drawn their own conclusions from the interview material of the entire therapy.

2. Data Analysis: Methods will be developed to organize the extensive material which will be gathered by a variety of partial, total, cumulative exposure techniques; to divide it into units which on the one hand

Project Description (cont'd)

accurately reflect the nature of the exceedingly complex interactions between patient and therapist, and on the other are sufficiently specific and manipulatable to permit an orderly and meaningful analysis of the therapeutic process.

Two training analysts have studied very intensively a short series of therapeutic interviews: first using a typescript alone, then the sound recording, and finally the sound motion picture. These studies were carried out independently at the beginning, but they are now being combined in order to set up categories for the individual elements which must be rated in order the study the therapeutic process.

In the early part of the project, the filmed therapeutic interviews which were studied by the group had been made at the University of Illinois School of Medicine where another research group working toward a similar goal had established close liaison with us.

In 1957 our own equipment was finally put in working order and an experienced therapist began a trial series of single interviews with a variety of patients and with several normal controls. In 1958, he began psychoanalysis with a suitable patient who had been referred to the Clinical Center by a local practitioner. At the time of this writing over 500 consecutive interviews have been recorded on sound film, and the work is continuing. The interviews have been cut down to two per week, and the terminal phase of therapy is being approached.

Work has continued on the development of methods which will permit a more precise definition of the changes which occur in the course of psychoanalysis. A number of different systems have been explored:

A. A dynamic analysis of two hours using three levels of data: (1) Typescript, (2) Tape, and (3) Sound Film. Each of these was gone over some 20 to 25 times to determine what new data comes with each level of communication and the possible significance of the areas of agreement and difference between trained observers.

B. A thematic summary which included the following items: (1) Topic, (2) Affect, (3) Referent, and (4) Time. It was the purpose of this study to develop a method of indexing which could be carried out by a research assistant,

Project Dexcription (cont'd)

which would enable the investigator to select out relevant material from any hour.

C. Microscopic analysis of several therapeutic hours, with particular reference to the interaction. In this study, a group of five investigators met twice weekly for a period of five months to review the hours selected. Sound recordings were played back repeatedly. Each hour was divided into very small units, their being more units than interactions. Each unit was treated according to: (1) Form (mode or style), (2) Conscious Motivation, (3) Unconscious Motivation, and (4) Implications for Relationship.

D. Macroscopic analysis of a series of hours. In this study we tried, (1) groupings into what might be called sub-themes, consisting of one to several statements of patient and therapist which seemed dynamically related; and (2) grouping into larger dynamically related clumps - in one hour there were nine such groups, which might be considered the themes of the hour. Each of these was then treated in the following terms: (1) Dynamics: (a) major areas of anxiety; (b) anxiety-fraught interactions; and (c) elements of strength and weakness of character revealed and defenses employed. (2) Mechanics of communication: (a) roles of each participant, and (b) facilitation or discouragement of each other's roles. (3) Consequences for relationships: (a) areas of success and failure of communication, (b) closeness versus distance of relationship, and (c) therapeutic versus non-therapeutic direction.

E. We are now engaged in the analysis of the first ten hours of a psychoanalysis, viewing the interaction under the following: (1) Essence of the hours, (2) Events related to previous hour or hours, and (3) Predictions of (a) immediate developments (b) major resistances, and (c) major conflicts. An interim report on these studies has been presented at a professional meeting; and a report is now being prepared for publication.

F. Kinesic Studies: (1) Foot movement. Two samples collected and analyzed, the first finding association between foot movement and speech disturbance at the .01 level, the second finding no association. A third sample has been collected, and is now being analyzed for speech disturbance. The variability in movement from interview to interview is so great as to cast doubt on its usefulness beyond a characteristic of the interview as a whole: the spread is from

Project Description (cont'd)

1 to 54 in 18 interviews so far studied. Thus while in those interviews with many movements, the occurrence of a movement may mean something about the events within the interview, interviews with very few movements may be best characterized as lacking in information, not lacking in the sort of disturbance we are interested in. It also is very clear that in later interviews there are more movements than in earlier ones, the first two samples having been selected within the first 40 interviews, and the third from 50 to 100. Work is now in progress sampling much later interviews for simple count of foot movements. One patient who produced few movements showed a pattern of alternation between movement and speech disturbance in the one interview which has been completely analyzed. A second patient moved so often as to contribute no information. We plan to do another interview of the informative patient to see if the pattern holds up. (2) Hand movement. Some preliminary studies have been carried out. Some movements are "gestural," that is, accompany speech as if for emphasis of important words. Others are shifts in position, much as there are postural shifts in people who are sitting up. Others are "nervous" movements, fidgets, or however these might be described - fingering a button on the blouse, lining up the tips of fingers, and the like. It is felt that the gestural movements do not give much information; they occur when the patient is talking and stops when he stops. Also they are somewhat seductive as to ascribing "meaning," since they are associated with talking.

G. Self-presentation. This work is an attempt to describe the way the person would like himself perceived by others at a given time in the interview. There is wide variability between patients as to how visible their self-presentations are. Fortunately for our preliminary work the Project's patient seems easy to code. But the proof of this ease will be in writing instructions for coding, and checking the reliability in using these instructions.

Major Findings: None as yet. Much methodological research must be done before substantive theoretical contributions can be made.

Significance: This is one of a series of studies of the psychotherapeutic process: The Process of Change and the Communication of Value Systems in Psychoanalytic Theory, M-P-P(C) 5; Body Movements as Expression of Changes in Psychological Tension Levels, M-P-C(C) 21; Analysis of the Psychotherapeutic Process: The Cumulative Information Derived from Repeated Viewing

Significance (cont'd)

of Comples Material, M-P-C(C) 2; and Development of an Ego-Integration Conceptual for Studying Psychotherapy, M-P-P(C) 6.

Despite the fact that psychotherapy is the major therapeutic device in psychiatric treatment, our understanding of it as a process is still very limited. One reason for this is that previously data could be secured only by the therapist; his reporting was limited both by the fact that he was a participant as well as an observer in the process and also by the human impossibility of reporting completely what had transpired. In the therapeutic situation, the relationship is exceedingly complex, and this is all the more true since much of the communication occurs at an implicit level. Hence, much of the significant data was not even available to anyone outside the relationship which it was proposed to study. The sound motion picture provides for the first time a sizable and significant amount of objective data hitherto unobtainable; what is equally important is that this data is collected in a form suitable to multiple and repeated analyses.

This series of studies may make many contributions methodologically. It will be possible to study the psychoanalytic process scientifically to a far greater degree than has heretofore been possible. Theoretically it is expected that it will make available new and highly significant data - data which are gathered in a naturalistic setting but which are as objective as those usually obtained in laboratory experiments.

Beyond the direct contribution to a better understanding of the psychotherapy process itself, this project may aid in the establishment of the scientific bases of psychoanalytic theory. Psychoanalysis may be regarded as one of the central socio-psychological sciences. It deals with man - with his in-born drives and abilities, and also with those changes in him which result from his gradual acculturation as he develops from infancy to childhood. Although it deals with the same kind of data with which the social sciences are concerned, it also provides unique information concerning the subjective aspects of the activity of the central nervous system. In this sense it constitutes a bridge to that fullest understanding of man which will come only when we can integrate our understanding of the interaction of social, biological, and genetic factors which determine the nature, course, and end result of his development.

Proposed Course of Project: It is expected that this program will continue for many years.

Part B. Honors, Awards, and Publications

Publications other than abstracts from this project:

Shakow, D.: The Recorded Psychoanalytic Interview as an Objective Approach to Research in Psychoanalysis. Psychoanal. Quart. 29: 82-97, 1960.

Parloff, M. B.: Communication of Values and Therapeutic Change. A.M.A. Arch. Gen. Psychiat. 2:300-304, 1960.

Parloff, M. B.: Communication of 'Therapy Values' Between Therapist and Schizophrenic Patients. J. Nerv. Ment. Dis. 130:193-199, 1960.

Parloff, M. B.: Patient-Therapist Relationships and Therapeutic Outcome. J. Consult. Psychol. (In Press).

Serial No. MCR(C)11, formerly MD(C)3
1. Child Research Branch
2. Clinical Investigations
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: A Follow-up Study of Skin Sensitivity, Muscle Strength, and Vigor of Response in Newborn Infants.

Principal Investigator: Richard Q. Bell

Other Investigators: D. Wells Goodrich

Cooperating Units: None

Man Years (calendar year 1960):
Total: 1.43
Professional: .33
Other: 1.10

Patient Days (calendar year 1960): None

Project Description:

Objectives:

To identify the neonatal precursors of orientation toward objects and action in space or toward non-hazardous play and close contact with adult protective figures as seen in preschool children.

Methods Employed:

Infants were accepted for study only if parents lived within easy driving range of NIH, planned to remain in the area for at least three years, and consented to bring in their child when near two and a half to our nursery school for follow-up study. Each of 29 male and 29 female newborn infants selected in this way were studied for three hours between feedings on two separate occasions prior to discharge from Suburban Hospital. When in a state of sleep, threshold for reaction to pressure stimulation of the skin was established with the Semmes-Weinstein aesthesiometer. When awake, strength of neck and back muscles was tested. Shortly before regular feeding time, rate and pattern of sucking was tested, as well as vigor and rapidity of response to interruption of sucking.

Major Findings:

In analysis of data from MD(C)3 males were found to react less to

Part A. (Continued)

a decrease in environmental temperature. They also showed greater muscle strength in neck and back. Potentially useful differential patterns of reaction to interruption of sucking were identified but were found not to show sex differences. The finding on reaction to reduction of temperature confirmed predictions based on previous studies and that on muscle strength replicated a previous finding.

This year another modality of cutaneous sensitivity has been tested using an aesthesiometer. The measure of muscle strength has been improved. Sex differences in the same direction have again been found, males showing higher thresholds and greater muscle strength. The aesthesiometer used provides relatively stable measures of the pressure threshold. It is expected that it will be possible to settle upon this device as a basic measure of general cutaneous sensitivity, though studies of other aspects are still needed. The new method of measuring muscle strength appears to have resulted in much better discrimination.

A method used in previous studies to categorize reaction of the infant to interruption of feeding has been improved so that it can be carried out with the great majority of infants with little difficulty. All methods developed in this study appear sufficiently reliable to justify a two and a half year follow-up study of later correlates. Furthermore, a reanalysis of results from the previous study indicates that sex differences in sensitivity to cutaneous stimulation and muscle strength are not due to trauma associated with greater vulnerability of males to the effects of perinatal complications.

Significance to the Program of Mental Health Research:

The patterns being studied offer a possible means of detecting genetically controlled or at least congenital factors which may affect human development. Attempts by other studies to identify such patterns in infants have led to confusing results due to perinatal factors which create illusory behavior patterns. Two of the three variables in this study, cutaneous sensitivity and muscle strength, show sex differences similar in direction to those found on adults, and are not related to brain damage associated with perinatal complications. This increases the probability that these variables are genetically controlled, are not artifacts of higher risk of brain damage in males, and are not likely to disappear shortly after the newborn stage. The third variable, efficiency of feeding and vigor of response to interruption of feeding, is not related to either of the other variables and does not show sex differences.

Part A. (Continued)

Interest in the findings on cutaneous sensitivity and muscle strength is motivated by an hypothesis developed from findings on primitive human cultures. This hypothesis is that male infants, due to greater muscle strength and higher thresholds to pain, touch, and temperature, are congenitally equipped for gross motility in space and relatively insulated from pain incident to trauma which might normally be expected to result from increased motility and environmental exposure. Care of offspring by the female is a role normally involving restricted motility and low risk of traumatic skin stimulation. Since some female newborns are more like the average male and vice-versa, the possibility exists that measures of skin sensitivity and muscle strength in the newborn may tap a genetic pattern contributing to differential development. Data from a retrospective study (MCR(C)10) provide some indication that this genetic pattern is related to whether the preschool child is oriented toward objects and action in space or toward non-hazardous play and close contact with adult protective figures.

Proposed Course of Project:

The present sample of newborn infants will be increased to approximately 45 of each sex by continuation of data gathering until March 1961. Families remaining in the area two and a half years from now will be contacted for enrollment of the child in our preschool research project (Serial No. MCR(C)10). Methodologies developed in this latter project will be used to relate variables measured in the newborn period to those measureable in the preschool period. This same project will serve as a means of validating the retrospective questionnaire used in the current preschool project, since it will make it possible to compare a mother's recollection of her two and a half year old child's characteristics as an infant with measures actually obtained in the newborn period by our own staff.

In addition to serving the above immediate purposes this project provides methods which will be applied to infants born to couples studied in a related project, MCR(C)12. Measurement of parent personality prior to pregnancy and infant characteristics prior to any extensive behavioral interaction with parents should make available two relatively independent sources of information. These sources are to be used to disentangle the otherwise very difficult picture of effects of parents and children on each other in normal growth.

Part B included Yes X No ____

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B Honors, Awards, and Publications

Publications other than abstracts from this project:

Bell, Richard Q., in "Recent Contributions of Biological and Psychosocial Investigations to Preventive Psychiatry." Proceedings of the Second Institute on Preventive Psychiatry, Ralph H. Ojemann (Ed.), State University of Iowa, 1959, Iowa City, Iowa.

Bell, Richard Q., in "Parent Education and the Behavioral Sciences: Relationships Between Research Findings and Policies and Practices in Parent Education." Grams, Armin (Ed.), Children's Bureau Publication No. 379, 1960, U. S. Department of Health, Education, and Welfare.

Serial No. MCR(C)10, formerly MD(C)2
1. Child Research Branch
2. Clinical Investigations
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Relationship of Preschool Behavior to Retrospective Reports of Neonatal Behavior.

Principal Investigator: Richard Q. Bell

Other Investigators: Harold L. Raush

Cooperating Units: None

Man Years (calendar year 1960):
Total: 6.36
Professional: .66
Other: 5.70

Patient Days (calendar year 1960): 1116

Project Description:

Objectives:

To obtain from mothers of preschool children retrospective reports of the child's characteristics as an infant and relate these to orientation toward objects and action in space or toward non-hazardous play and close contact with adult protective figures as seen in the behavior of the preschool child.

Methods Employed:

Twenty-three aspects of the behavior of infants in the first month were obtained by questionnaire from 60 mothers of preschool males. From this sample a sub-sample of 43 cases was selected, all being born without perinatal complications and free of significant developmental abnormality as it was possible to ascertain this from the mother. The 23 measures for these 43 cases were subjected to a factor analysis. Two major factors emerged. One of these involved variation from fast, efficient, steady feeding and vigorous, rapid reaction to interruption of feeding through to lethargic, inefficient feeding and weak response to interruption of feeding (oral factor). The other factor involved variation from positive reaction to physical contact initiated by the mother, rapid rate of falling asleep and deep sleep through to lack of response to contact, slow rate of falling asleep and shallow sleep (skin-sleep factor).

Part A. (Continued)

Children scoring at or beyond the 33rd percentile on both of these factors were selected for study in our nursery school. The sample was augmented by an additional 80 cases scored on the same two factors in order to obtain 43 children meeting the requirements for the study and able to attend during one of the seven one-month nursery school sessions. During 20 days of attendance at the nursery school the children were rated by a male and female nursery school teacher and were observed by time sampling methods by four observers. With the exception of one case, all ratings and observations were made without knowledge of the factor scores on the infancy measures. The factor scores were related to the ratings and observations in order to obtain leads for a two and a half year follow-up study on a sample of newborn infants whose characteristics are being assessed by our own staff rather than by retrospective report MCR(C)11.

Major Findings:

At the time of this report it has only been possible to complete a preliminary screening using short-cut methods rather than more time consuming and valid statistical tests. The latter await reworking a computer program designed to test for relationships between the factor scores and 120 rating and observation categories. The computer program resulted in erroneous output and its correction is still pending. The results of the preliminary screening, subject to correction when full statistical treatment has been completed, are as follows. Children scoring high on the oral factor showed more vigor of application to play and had more falls and accidents. They ate larger breakfasts at home, ate rapidly in our nursery school, and were active during rest periods. They showed less interest in initiating contacts with nursery school teachers, except as this was necessary in order to obtain play materials, and smiled less at teachers or peers. Their play was more continuous. They imitated the play of other children more frequently. When blocked by other children they tended to handle the problem themselves by direct action rather than protesting or seeking help from a teacher. Children scoring high on the skin-sleep factor more often initiated physical contact with teachers, reacted more positively to contact by teachers, and were soothed more when upset if held by teachers. They showed a general caution and a preference for non-hazardous play, were more distracted from play by adjacent activities of others, spent more time watching the play of others while not participating, were blocked or interrupted in play more by other children, and showed more disorganization of play when interrupted. Their play was imitated less by other children. They ate less in the nursery school and dawdled with what food they did eat.

Part A. (Continued)

Significance to the Program of Mental Health Research:

Retrospective reports by mothers, though subject to a number of sources of error, offer an advantage over measurements of newborn characteristics obtained by our staff in the brief period an infant is in the hospital. They are based on longer term contact. The questionnaire used in this study is intended to reduce error due to defective recall, halo effects, inadequate subjective norms, and sex-stereotypes by using only mothers with two or more young children and using a special scaling technique involving comparison of like-sex children on very specific items of infant behavior. Direct observation of infants by our own staff has the advantage of objectivity and precision but is subject to the variability shown in the brief newborn period. Since errors involved in each approach are different, use of both approaches together provides a means of obtaining more valid information. The current study is an effort to validate the questionnaire by relating it to preschool behavior. To the extent that this is successful our program of research will be able to work back and forth between the more rapid retrospective research and the more time consuming longitudinal studies. Both approaches are designed to elucidate congenital factors contributing to human development, as discussed in a related project, MCR(C)11.

Proposed Course of Project:

In the next two years an additional male sample and a female sample will be studied. A separate factor scoring will be carried out for the female sample. Following completion of these studies, infants studied in the newborn period by our own staff (MCR(C)11) will have reached age two and a half and will be enrolled in the nursery school for study using the methods developed up to that point. Eventually it will be possible to study children in our nursery school who have been studied in the newborn period by our staff and whose parents were studied in the pre-conceptual period in MCR(C)12.

Part B included Yes X No _____

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B Honors, Awards, and Publications

Publications other than abstracts from this project:

Bell, Richard Q., In Proceedings, Twenty-Fifth Anniversary Meeting, Society for Research in Child Development, Child Developm., Vol. 31, 187-239, 1960.

Bell, Richard Q., (Chairman), Direct Study of Child-Parent Interactions, Workshop, Amer. J. Orthopsychiat., Vol. 30, No. 3, 445-467, 1960.

Bell, Richard Q., Retrospective and Prospective Views of Early Personality Development, Merrill-Palmer Quarterly of Behavior and Development, Vol. 6, 131-144, 1959-60.

Serial No. MCR(C)12, formerly MD(C)4
1. Child Research Branch
2. Clinical Investigations
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A:

Developmental Patterns in the Young Family (TITLE)

Principal Investigators: D. Wells Goodrich, M.D.
Harold L. Raush, Ph.D.

Other Investigators: Richard Q. Bell, Ph.D.; Paul Blank, M.S.W.; John Campbell, Ph.D.; Arden A. Flint, M.D.; Walter Sceery, M.S.W.

Cooperating Units: Laboratory of Socioenvironmental Studies

Man Years:

Total: 7.20 Patient Days: 100

Professional: 5.20

Other: 2.00

Project Description:

Objectives:

1. To explore patterns of interpersonal behavior, communication and affect within the initial marital relationship in newlywed couples, as a basis for a longitudinal study of the first years of family development.

2. To explore aspects of the initial marital adaptation patterns, and of the personality development of each spouse, which are hypothesized to relate systematically to specific patterns of parent-infant behavior to be observed (at a later phase of the project) during the initial adaptation of the couple to their firstborn infant. These specific patterns include the attitudes and behaviors of the couple in situations of feeding and of affectional physical contact.

Part A (continued)

Method Employed:

The newlywed couples are studied by means of joint home interviews, individual interviews, direct observations of marital interaction and questionnaires. These methods are designed to assess the current areas of satisfaction and conflict in the marriage; the sequence of adaptation by the couple to the developmental tasks of initial marital adjustment; the degree of emotional commitment by the couple to the marriage in situations of disagreement; the process of decision making by the couple used in new and stressful situations; the prospective images of parenthood during the neonatal period; and each spouse's images of the developmental relationships with his or her parents. In addition, data on each spouse's changing percepts of husband and wife roles are being assessed at times when major changes are taking place in the family.

Patient Material:

Couples living in the community who are not being treated for any major disorder of personality are accepted on a voluntary basis for study. To date, in the course of developing methodology, the project has had contact with 40 such volunteer couples.

Major Findings:

During the past year the work of the project has been devoted to developing methods and hypotheses. During the second year, a few findings may become available, although it is anticipated that two more years will be required for most findings on initial marital adjustment to become available.

Significance:

This project is unique in attempting to obtain data on the characteristics of parents prior to the actual experience of child rearing. It thus avoids one major shortcoming of most studies in this field, the fact that investigators with customary research designs cannot differentiate the effects of a child on the parent from the effects of parents on the child. Study of the period of early marriage prior to the first pregnancy is important in view of the basic need in preventive mental health for an understanding of the precursors of later normal and abnormal outcomes of family development.

Evidence from many sources has emphasized the crucial importance to later ego strength of the earliest years of personality development. Recent theory and clinical practice has been

Part A (continued)

increasingly concerned with the family unit as a potent influence, together with genetic factors in the infant, for determining personality development. The interactional effects of these genetic and early family determinants of personality have been studied for the most part retrospectively and in disordered personalities and not sufficiently by prospective and direct observational methods with well functioning married couples. By utilizing the prospective and direct observational approaches, as well as retrospective data, this project is in a favorable position to clarify the significance of certain forms of initial marital adaptation as precursors of later patterns of family development. In particular, the project is exploring in newlywed couples the precursors to parental patterns of handling the oral and the physical contact factors in the newborn, factors described in MCR(C)11.

Proposed Course:

During the coming year we anticipate completing a pilot study of 40 newlywed couples. The development of methods for studying the triadic father-mother-infant relationship during the neonatal period following the birth of the firstborn child will be initiated. Preliminary findings on certain aspects of initial marital adaptation may become available.

Part B included Yes X No ____

Part B:

Honors, Awards and Publications:

Publications other than abstracts from this project

Goodrich, D. W., and Dittmann, A. T. Observing Interactional Behavior in Residential Treatment. AMA Archives of General Psychiatry, 2: 421-428, Apr. 1960.

D. Wells Goodrich, M.D. Structure and Process in the Primary Crises of Personality Development. Address delivered to the Second Meeting of the International Association for Child Psychiatry and Allied Professions, Cambridge, Mass., Feb. 10, 1960.

D. Wells Goodrich, M.D. The Provocator and the Therapist. Lecture to the Department of Psychiatry, University of North Carolina Medical School, Chapel Hill, N. C., March 26, 1960.

D. Wells Goodrich, M.D. Possibilities for Preventive Intervention During Initial Personality Formation. Chapter in the book, Possibilities of Prevention of Mental Disorders in Childhood, by Gerald Caplan, M.D., Editor, Harvard School of Public Health, Boston, Mass., June 8, 1960.

Serial No. M-P-C-(C)-1
1. Laboratory of Psychology
2. Section of the Chief
3. Bethesda

PHS--NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Administration of Laboratory of Psychology (A Joint Operation of the Clinical Investigations and Basic Research Programs)

Principal Investigator: David Shakow

Other Investigators: None

Cooperating Units: None

Man Years:
Total: 2.60
Professional: .60
Other: 2.00

Patient Days: None

Project Description:

Objectives: A. To maintain an administrative structure which will provide the optimum of communication with (1) Chief of the Laboratory, (2) among members of a section, (3) within the Laboratory as a whole, (4) and with other investigators and units in NIMH and other Institutes, and at the same time result in the least interference with the objectives and available time for research of individual investigators.

B. To complete organization of Laboratory.

Methods Employed: A. To achieve optimal administrative structure: Organization into a reasonable number of sections, conduct individual conferences with investigators, hold the minimal necessary number of meetings with individual section chiefs and with the group of Section Chiefs in the Laboratory as a whole.

B. To complete the organization: Recruitment of additional personnel.

Major Findings:

1. Personnel by Sections (Professional):

Part A.

Major Findings (Cont'd)

Clinical Investigations Program:

Office of the Chief

Shakow, David (Chief)
Bergman, Paul
Dittmann, Allen
Kendig, Isabelle
Rosenthal, David
Zahn, Theodore
Waskow, Irene (NIMH Fellow from 10/59)

Section on Child Development

Bayley, Nancy (Chief)
Gewirtz, Jacob (L.A.)
Rheingold, Harriet
Schaefer, Earl

Section on Personality

Parloff, Morris (Chief)
Boomer, Donald
Caron, Albert
Handlon, Joseph
Unger, Sanford

Basic Research Program:

Section on Aging

Birren, James (Chief)
Botwinick, Jack
Jerome, Edward
Streicher, Eugene
Warren, Richard

Part A.

Major Findings (Cont'd)

Section on Animal Behavior

Rosvold, H. Enger (Chief)
Mirsky, Allen
Mishkin, Mortimer
Szwarcbart, Maria
Brown, Thomas (NIMH Fellow from 1/60)
Butter, Charles (NIMH Fellow from 9/59)
Lodge, Ann (NIMH Fellow from 10/60)
Robinson, Brian (R.A. 3/59)

Section on Perception & Learning

Carlson, Virgil (Acting Chief)
Calhoun, John
Barbehenn, Kyle (NIMH Fellow from 1/59)

2. Program of administrative conferences held by Chief of Laboratory.

Proposed Course of the Project:

1. In the context of the discussion of a new building, the efforts to recruit a Section Chief for Perception and Learning was reopened during the year. A Committee of Section Chiefs is now at work on the problem.

2. Because of certain present limitations in our own Clinical Center facilities, it has been necessary to attempt to find settings outside which would provide us with the needed subjects. This year the problem has been particularly prominent in the schizophrenia area where we have needed acute patients and additional chronic patients. Although some progress has been made towards obtaining such patients elsewhere (particularly at St. Elizabeth's) the arrangements are not economical of time and energy. It was our hope that the generally felt need for an acute schizophrenia service at the Clinical Center would be met during the past year. This has not happened but we are still hopeful. In the Child Development area relief has been obtained for some aspects of the program through the setting up of the Center for Biosocial Growth. However, we must continue to carry out a considerable portion of our studies elsewhere, and the need for a child laboratory is still great.

Part A.

Proposed Course of the Project (Cont'd):

3. The present year has seen continued maintenance of facilities for post-doctoral fellows. This has been very gratifying for both us and the fellows and we are encouraging the continued recruiting of this level of personnel.

Part B included: No.

Serial No. M-P-C-(C)-3.
1. Laboratory of Psychology
2. Section of the Chief
3. Bethesda

PHS--NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Psychology of Schizophrenia

Principal Investigator: David Shakow

Other Investigators: David Rosenthal, Theodore Zahn

Cooperating Units: Unit

Man Years:
Total: .96
Professional: .30
Other: .66

Patient Days: None

Project Description:

Objectives: To bring together a large body of experimental data on schizophrenia collected over many years into a series of monographs developing a theory of the psychology of schizophrenia centered around the concept of segmentalization. A detailed analysis of the body of experimental data already available and of new data to be gathered on our wards here and at St. Elizabeth's (see Project Descriptions M-P-C-(C)-14, 15, 16, 17, 18, 24) will be carried out to test certain hypotheses as to the importance of difficulties arising particularly during the period of preparation for response in schizophrenics.

Methods Employed: In relation to the already accumulated material, ranging in complexity from studies of the latent time of the patellar tendon reflex to studies of social response, the usual methods of statistical and conceptual analysis will be utilized. Some new developments deriving from studies of Phillips, Rodnick and Garmezy regarding good and poor prognosis, and certain other studies on "reactive" as opposed to "process" schizophrenics will be utilized for further differentiation of the material. Several related studies are being carried out on senescent and brain damaged subjects and they will be used in this study for control purposes.

Patient Material: For this particular study no patient material will be required except for the data already collected in past studies and current studies described under other projects (see Projects M-P-C-(C)-14, 15, 16, 17, 18, 24).

Part A.

Major Findings: During the year additional progress was made in the available data in several areas. This was done in the context of the preparation of a paper for the XVIth International Congress of Psychology at Bonn in August 1960 on "Psychology of Schizophrenia: Basic Adaptational Factors" and the preparation of the Geroge Kirby Collier Memorial Lecture at the University of Rochester in December, 1960 on "Some Aspects of the Psychology of Schizophrenia."

Scientific Significance of the Program to Mental Health Research: The studies mentioned above contribute to the understanding of the psychology of schizophrenia and eventually to a comprehensive theory of schizophrenia.

Part B included: Yes.

Part B. Honors, Awards, and Publications.

Publications other than abstracts from this project:

Rosenthal, D., Lawlor, W. G., Zahn, T. P., and Shakow, D.: The relationship of some aspects of mental set to degree of schizophrenic disorganization. J. Pers. 28: 26-38, 1960.

Publications other than abstracts not related to this project:

Shakow, D.: The recorded psychoanalytic interview as an objective approach to research in psychoanalysis. Psychoanal. Quart. 29: 82-97, 1960.

Honors and Awards, not related to this project:

Dr. David Shakow was presented the Division of Clinical Psychology, American Psychological Association Award, 1959, for "distinguished contribution to the science and profession of clinical psychology."

Serial No. M-P-C-(C)-5
1. Laboratory of Psychology
2. Section of the Chief
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Judgment of affective expression from short sequences of motion picture film.

Principal Investigator: Allen T. Dittmann

Other Investigators: Donald S. Boomer and Morris B. Parloff

Cooperating Units: None

Man Years (calendar year 1960):		Patient Days (calendar year 1960):
Total:	.3	0
Professional:	.2	
Other:	.1	

Project Description:

Objectives: This project was reopened this year to test the technique of the Affect Checklist further. The technique had been developed as a measure of expression of affect from short (i.e., 3 seconds) sequences of motion pictures of subjects. Judges checked those affects on the checklist which seemed appropriate, and these checks were scored according to the three factors which resulted from a centroid factor analysis of the checklist. In applying these scores to interview material, 48 3-second excerpts were used, half preceding and half following each of 24 therapist interventions from two interviews. The therapist interventions were independently rated as to Depth of Interpretation. The results were only of borderline significance; they are thus less interesting from a substantive than from a methodological point of view. In the course of this work an extension of the method was begun, with the specific research design devised by Dr. Boomer. This extension was developed to take account of the complications of the judgments: many of the excerpts were judged unreliably, and we felt that in many instances the unreliability had to do with conflicting "messages" being sent by the subject in the pictures. Facial expression, for example, might be judged one way, while posture, or hand movements would belie that judgment. In three seconds, a judge would not be able to integrate these conflicting messages, and reliability of the judgments would suffer. In viewing a few of the excerpts repeatedly 5 to 10 times, we found that judges could have

Part A

Objectives (Continued): time to formulate their impressions, and take better account of the complications of the communication.

Methods Employed: Considering "Channel 1" to be facial expression, and "Channel 2" to be expressions of other parts of the body, Experimental excerpts will be chosen to present incompatible expressions from the two channels, and Control excerpts will be chosen to match the experimental ones in Channel 1, but show compatible expressions in Channel 2. The first test will be whether the experimental excerpts are judged differently from the controls, and next, whether on repeated viewings the judges will be able to specify the cues which led to the judgments.

Excerpts are currently being selected, using a wide variety of persons depicted in the motion pictures. For the initial trials we shall select excerpts which vary along the dimension of pleasant-unpleasant affect, which is the first dimension in a number of factor-analytic studies of affect. The length of the excerpts will be chosen empirically, preliminary trials pointing to 5-10 seconds as the range.

Major Findings: This study is in the data-collection stage, and no results can be reported at this time.

Scientific Significance to the Program of Mental Health Research: This study will have significance both from a theoretical and from a practical standpoint. On the theoretical side, it will test a general working hypothesis held by many in the field of expressive movement. Previous studies have shown that in general there is unity in expression over many modes of expression - facial expression, gait, posture, and the like. But incompatibility among expressions in different modes is postulated to occur when conflict is present. Such incompatibility has been shown in a few instances, but has never been demonstrated in a systematic study.

From the practical point of view, we hope this study will result in a more refined technique for determining conflict situations in interviews, which may then be related to other factors, such as the content of the interview, the interaction between interviewer and interviewee, the stage of psychotherapy, and the like.

Proposed Course of Project: To carry out the study as planned.

Part B included No

Serial No. M-P-C-(C)-8
1. Laboratory of Psychology
2. Section of the Chief
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: The self-concept and body image as related to disease susceptibility and organ choice.

Principal Investigator: Isabelle V. Kendig

Other Investigators: None

Cooperating Units: National Institute of Arthritis and Metabolic Diseases; National Cancer Institute

Man Years (calendar year 1960):

Total:	1.00
Professional:	.5
Other:	.5

Patient Days (calendar year 1960): 9

Project Description:

Objectives: To explore attitudinal factors affecting health and longevity. More specifically, to investigate the experiences of early childhood and adolescence and the attitudes inculcated which are instrumental in determining the nature of the self-concept and the body image in relation to susceptibility to illness, organ choice and outcome of disease.

Methods Employed: Extensive use of self-concept tests and a variety of projective techniques, including the Rorschach, Draw-a-Person, and Four Picture tests with patients proved unsatisfactory, the results reflecting only the present self-concept and body image as unfavorably modified by years of illness. A detailed interview schedule was therefore developed to uncover the attitudes toward the self and the body inculcated in childhood and adolescence, explicitly by direct instruction and implicitly through life experiences and through the emotional climate of the home and family reactions to illness, which might bear a relation to subsequent disease susceptibility. This instrument, pretested on groups of patients and 'normal' controls, was then revised and expanded, scales drawn up and a system of weights devised for scoring responses. The notable development in 1960 has been the completion and scoring of the interview protocols of both patients and controls. The sample includes 50 arthritic and 25 leukemia patients with controls drawn from

Part A

Methods Employed (Continued): NIH personnel, individually matched on six variables - race, sex, age, education, occupation and religion. The completed sample totals 149 cases, a single leukemia patient proving difficult to match. Of these cases, 104 have been scored by trained independent workers as well as by the principal investigator with inter-scorer reliability of .91.

Patient Material: Patients in this study were drawn from the National Institute of Arthritis and Metabolic Diseases and from the National Cancer Institute.

Major Findings: There are no substantive findings to be reported at this time as the completed data is only now being analyzed with the help of the Computation and Data Processing Branch.

Scientific Significance to the Program of Mental Health Research: To the extent to which the results of this study may throw light on the part which beliefs and attitudes to the self and to the body play in relation to subsequent health and longevity, it should have value in forwarding the work of the various Institutes in which it is carried on. It should also tie in with studies in progress in the Laboratory of Psychology, specifically in the fields of child development and gerontology. In these areas it will be significant to trace the rise, modification and deterioration of the self-concept over time in its effect upon resistance to disease.

Proposed Course of Project: The goal now in sight is to complete the analysis of the data and embody whatever positive or negative findings there may be in a final report.

Part B included No

Serial No. M-P-C-(C)-9
1. Laboratory of Psychology
2. Section of the Chief
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Precocious Puberty and Pseudohermaphroditism.

Principal Investigator: Roy Hertz, M.D.

Other Investigators: Isabelle V. Kendig

Cooperating Units: National Cancer Institute

Man Years (Calendar year 1960):

Total:	0.0
Professional:	0.0
Other:	0.0

Patient Days (Calendar year 1960): 0

Project Description:

This project can be considered dropped since no new patients were referred to us during the current year.

Part B included: No.

Serial No. M-P-C-(C)-12
1. Laboratory of Psychology
2. Section of the Chief
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Studies of heredity and environment in the etiology of schizophrenia. (Formerly Schizophrenic illness in a set of identical quadruplets.)

Principal Investigator: David Rosenthal

Other Investigators: None (Formerly numerous NIMH investigators)

Cooperating Units: None (Formerly Nursing Unit, 3 West)

Man Years (calendar year 1960):		Patient Days (calendar year 1960):
Total:	1.00	0
Professional:	.50	
Other:	.50	

Project Description:

Objectives: This project is really a continuation and outgrowth of a study on schizophrenic illness in a set of identical quadruplets. The study involves the problem of how hereditary and environmental factors interact to make for schizophrenic outcomes of varying degree and quality. To deal with the problem effectively, it is important to understand and apply knowledge previously gained by other investigators. A critical examination of the literature has been required to determine what knowledge is firm and what new knowledge can be gleaned from a circumspect overview and integration of many previously unrelated kinds of data. Such knowledge not only provides a solid basis for analyzing schizophrenia in identical quadruplets, but is necessary for the intelligent planning of further studies in this area, which we are beginning to do.

Methods Employed: 1. A constructively critical, hypothesis-oriented analysis of the worthwhile literature on heredity and environment in schizophrenia. 2. A series of studies (genealogical, psychiatric, physiological, genetic, psychological and sociological) of the family with schizophrenic identical quadruplets is being prepared by a number of investigators and myself, and I will integrate the various studies, viewing their relevance to the heredity-environment question. 3. Families of schizophrenics are being given a battery of tests of

Part A

Methods Employed (Continued): thinking, to see if certain patterns of thinking anomalies are transmitted in these families.

Patient Material: 1. A set of MZ quadruplets and their parents. 2. Parents and siblings of schizophrenic and non-schizophrenic subjects.

Major Findings: 1. The analysis of the literature is being reported in a series of papers, two of which are now published; a third is in press. 2. A monograph on the family with MZ quadruplets is in preparation. 3. Families of schizophrenic and control subjects will continue to be tested for some time to come.

Scientific Significance to the Program of Mental Health Research: It is hoped that these studies will help to unravel one of the knottiest and most important problems of psychopathology: what behaviorally is inherited and what is learned which in combination make for schizophrenic reactions of different kinds?

Proposed Course of Project: 1. Several additional papers on the relevant literature are either in preparation or in the planning stage. These will continue as long as they continue to fill important gaps in our knowledge. 2. It is hoped that the first draft of a monograph on the family with MZ quadruplets will be completed by the end of 1961. 3. Studies of thinking anomalies in families of schizophrenics will be continued for some time. 4. Other studies in this problem-area are being contemplated and may be initiated after 1961.

Part B included Yes

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B. Honors, Awards and Publications

Publications other than abstracts from this project:

Rosenthal, D.: Confusion of identity and the frequency of schizophrenia in twins. A.M.A. Arch. Gen. Psychiat. 3: 297-304, 1960.

Rosenthal, D.: Sex distribution and severity of illness in samples of schizophrenic twins. J. Psychiatric Res. (In Press).

Serial No. M-P-C-(C)-14
1. Laboratory of Psychology
2. Section of the Chief
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Integrative processes in schizophrenia. (Formerly The measurement of schizophrenic disorganization.)

Principal Investigators: David Rosenthal

Other Investigators: David Shakow, Theodore P. Zahn, and others cooperating in special studies.

Cooperating Units: U.S. Naval Medical Center, St. Elizabeth's Hospital, and Clinical Center Wards.

Man Years (calendar year 1960):		Patient Days (calendar year 1960):
Total:	1.00	0
Professional:	.50	
Other:	.50	

Project Description:

Objectives: To study cognitive, perceptual and attentional processes in schizophrenic subjects. These are not viewed separately, but as interrelated processes involving the highest levels of integration. We are also concerned with levels of disintegration and their measurement, relating deficits or anomalies in cognitive, perceptual and attentional processes to such levels of disorganization.

Methods Employed: Various kinds of experiments using different equipment and materials are used, depending on the particular experiment. In studies of thinking, we have thus far used the Object Sorting Test, a Concept Association Test, and a Concept Discrimination Test. We are also planning to use a modification of the Logical Analysis Device with Dr. E. Jerome. In studies of perception we have used the Taylor Perceptual Closure Scale and a Perspective Allusion Test. In studies of attention and mental set, we have used simple reaction time. To measure degree of disorganization, we have employed a paired comparisons technique.

Patient material: Acute and chronic schizophrenics, patients with acute reactions which are not schizophrenic, and normal controls.

Part A

Major Findings: 1. Chronic schizophrenics do not show perceptual closure to the same degree that normal Ss do. 2. Degree of disorganization can be measured with a high degree of reliability.

Scientific Significance to the Program of Mental Health Research: We hope to delineate in fair detail the nature of schizophrenic deficit at the highest integrative levels, and to show how these aspects of deficit reflect mutual influences and relationships of thinking, perception and attention.

Proposed Course of Project: We see this project as a continuing, long-term series of studies, each building on the ones preceding.

Part B included

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B. Honors, Awards and Publications

Publications not directly related to this project:

Rosenthal, D., Lawlor, W. G., Zahn, T. P., and Shakow, D.: The relationship of some aspects of mental set to degree of schizophrenic disorganization. J. Pers. 28: 26-38, 1960.

Serial No. M-P-C-(C)-15
1. Laboratory of Psychology
2. Section of the Chief
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Reaction time of schizophrenics.

Principal Investigator: Theodore P. Zahn (formerly David Rosenthal)

Other Investigators: David Shakow, David Rosenthal, Rue L. Cromwell, Visiting Scientist.

Cooperating Units: Clinical Sciences Laboratory (Wards 2-W and 4-W) and Clinical Neuropharmacological Research Center.

Man Years (calendar year 1960):		Patient Days (calendar year 1960):
Total:	1.0	49
Professional:	.5	
Other:	.5	

Project Description:

Objectives: Reaction time has been well established as a method for studying the acquisition and maintenance of preparatory sets. The object of this project is to investigate some of the variables governing the acquisition and maintenance of sets in schizophrenic patients on the assumption that these preparatory set factors play a major role in the deficits in the performance of schizophrenics.

Methods Employed: A standard reaction time method is used in which the subject's task is to lift his finger from a telegraph key as quickly as possible following a stimulus. The stimulus is presented at varying intervals after a warning signal which in most experiments occurs almost immediately after S depresses the key. The interval between the warning signal and stimulus is the preparatory interval (PI) and can be constant for a series of trials (regular procedure) or variable from trial to trial (irregular procedure).

Patient Material: Schizophrenic patients from Ward 2-W and from St. Elizabeths and D.C. General Hospital. Normal controls from Ward 4-W and from the St. Elizabeths Hospital staff.

Part A

Major Findings: 1. One experiment, the results of which we have replicated this year, showed that using the regular procedure, if series of trials with PIs of, say, 1, 2, 3, 7, and 15 seconds are given in that order RT is an increasing function of PI length and the curve is significantly steeper for schizophrenics than for normals. If, however, the series of PIs are presented in the reverse order - long to short - the schizophrenics in contrast to the normals do not improve their performance on the short PIs but remain at the "long PI level" of RT.

2. Another experiment, in which we replicated our previous results, involved the irregular procedure. Here RT is a decreasing function of PI length, the curve being steeper for the schizophrenic patients. This we found to be independent of baseline level of RT. We have found that the PI of the preceding trial (PPI) is an important variable in this procedure. If the PPI is shorter than the PI, RT will be shorter than if the PPI is longer than the PI. This effect was found to be greater in the patients than normals. Thus the schizophrenics are influenced more by the immediate PI and PPI than by the nature of the entire sequence of PIs as compared to the controls.

3. In another study we were concerned with the question of whether the disproportionately long RTs of schizophrenics to long PIs in the regular procedure was due to the slow tempo of events under these conditions or whether it had to do specifically with the maintenance of preparation to respond. Trials with short PIs and long intertrial intervals were compared with a condition in which the spacing of trials was the same but the PI was long and intertrial interval was short and one in which both intervals were short. The results showed that the long intertrial interval produced no detrimental effects on RT in either schizophrenics or normals whereas the long PI produced the usual disproportionate slowness in the patients.

4. In another experiment schizophrenics and normals were allowed to program the sequence of PIs however they pleased (autonomy) and this was compared with a condition where the same sequence of intervals was administered by the experimenter (control). In contrast to the normals the patients preferred and performed better on the control conditions than on the autonomy conditions.

5. The effects of two phenothiazine compounds on RT was studied. Both trifluoperazine and prochlorperazine improved RT and the "set index" developed by Rodnick and Shakow as compared to a placebo, but the improvement occurred mainly in patients with very poor performance under control conditions.

Part A

Major Findings (Continued):

6. Data published by two other investigators were reanalyzed to show that schizophrenics demonstrate a disproportionate slowness of verbal reaction time as compared to manual reaction time. This is interpreted as reflecting the schizophrenics' peculiar difficulty in interpersonal relationships.

Scientific Significance to the Program of Mental Health Research: These studies have given us new insights into some of the variables affecting the acquisition and maintenance of preparatory sets differentially in schizophrenics and normals. At the same time they have suggested new hypotheses some of which may be testable by means of concurrent psychophysiological recording.

Proposed Course of Project: As indicated above we hope to try repeating some of these studies while concurrently recording variables such as GSR, heart rate, finger volume, EEG, and EMG. We also plan to investigate the effects of other variables such as motivation, practice and the probability of PIs of different lengths.

Part B included: Yes

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B. Honors, Awards and Publications

Publications other than abstracts from this project:

Rosenthal, D., Lawlor, W. G., Zahn, T. P., and Shakow, D. The relationship of some aspects of mental set to degree of schizophrenic disorganization. J. Pers. 28: 26-38, 1960.

Serial No. M-P-C-(C)-17
1. Laboratory of Psychology
2. Section of the Chief
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Psychophysiological Responsivity in Schizophrenia.

Principal Investigator: Theodore P. Zahn

Other Investigators: David Rosenthal, William G. Lawlor (Special Consultant)

Cooperating Units: Clinical Sciences Laboratory (Wards 2W and 4W) and Clinical Neuropharmacology Research Center.

Man Years (calendar year 1960):

Total:	.75
Professional:	.25
Other:	.50

Project Description:

Objectives: To investigate arousal and responsivity in schizophrenic patients at the level of autonomic functioning. To determine what differences, if any, exist between schizophrenic patients and normals in baseline level, spontaneous variability, and the strength and habituation of the autonomic orienting response to simple stimuli. To determine what other aspects of behavior and personality these aspects of autonomic activity may be related to.

Methods Employed: Continuous measurement of the galvanic skin response (GSR), heart rate and respiration during repetitive presentations of auditory and visual stimuli. Ratings of several behavioral attributes have been made of some patients and controls by nurses, aids and psychiatrists using a method of paired comparisons. Other patients have been evaluated by ratings by two psychiatrists on a modified version of the MSRPP ("Lorr scale") on the basis of short interviews. The MMPI has been and will be given to most of the normal controls.

Patient Material: Data have been collected and analyzed on 32 patients and 16 normal controls. Data on an additional 20 patients have been collected and are being analyzed. Data on 20 NIH employees (controls) are being collected.

Part A

Major Findings: Data for the GSR which have been analyzed for 32 patients and 16 normal controls indicate:

1. In comparison to normals, patients give slightly fewer specific and more non-specific GSR responses. The ratio of specific to non-specific responses is much greater for the normals, however.

2. GSR baseline resistance is higher for normals. For this group it seems to show an initial drop with the onset of the stimulation and subsequent rise. For the patients neither the initial drop nor subsequent rise are clearly manifested. However, the patients show a rise in resistance from one session to the next in contrast to the normals.

3. The amplitudes of the GSR responses given to the stimuli are greater for normals, when measured either as a change in resistance or a change in log conduitance.

4. Habituation of responses seems slower for the patients. However, further analysis suggests that this may be due to a large group of patients who give very few responses to start with and a smaller group who give very many responses at the beginning of a session and don't habituate rapidly.

5. A relationship between ratings of "mental health" or "ego intactness" was found in one group of patients but not in a second. In the latter group, however, "mental health" correlated significantly with baseline resistance and response amplitude.

6. Heart rate data, which have been analyzed only for one group of 11 patients, show the response to the auditory stimulus to be a small drop in rate followed by a larger rise reaching a peak from three to five beats after the stimulus. This response is manifested significantly only to the auditory stimulus and more often by subjects with basal heart rates of below 80 beats per minute.

Scientific Significance to the Program of Mental Health Research: The data indicate a higher level of autonomic arousal under basal conditions which may or may not be due to the effect of the experimental situation. Combined with this is a diminished responsivity to the specific events in the situation. This suggests one possible reason for inadequate performance by schizophrenic patients in a wide variety of tasks. The present research is yielding methodological techniques which can be used to study autonomic functioning during the performance of tasks such as reaction time and it can also be considered as a baseline condition with which to compare these studies.

Part A

Proposed Course of Project: Further collection and analysis of data on the groups mentioned above in an attempt to corroborate present findings. We hope to investigate the orienting response more thoroughly using EEG and plethpographic techniques in order to attempt to replicate certain findings by Russian investigators and to use these techniques with schizophrenic patients. We also plan to record autonomic responses during the performance of tasks as indicated above.

Part B included No

Serial No. M-P-C-(C)-21
1. Laboratory of Psychology
2. Section of the Chief
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Body movement as expressions of changes in psychological tension states.

Principal Investigator: Allen T. Dittmann

Other Investigators: None

Cooperating Units: None

Man Years (calendar year 1960):		Patient Days (calendar year 1960):
Total:	1.1	0
Professional:	.5	
Other:	.6	

Project Description:

Objectives: To explore the relationships between body movements in psychotherapeutic interviews and changes in psychological tension states as measured by other means. Last year this project concentrated on the relation between foot movements and speech disturbances on the theoretical grounds that both are modes of discharging emotional tension relatively removed from intentional control, and should thus occur together. There were three samples drawn from a wide range of interviews with one patient. The first sample confirmed the hypothesis, and the second did not. This year the analysis of the third and largest sample was completed, with completely equivocal results. It was our conclusion that conceptualization of emotional expression was not yet at the level where rational research, with advance hypotheses, could be the rule, and we therefore turned to a more empirical approach, using the criterion group method and counting a number of kinds of body movement.

Methods Employed: The criterion groups were excerpts of interviews representing different moods of a single patient. These moods were selected to represent the most frequently occurring moods as stated by the patient. These were initially "jittery," "angry," and "gloomy," with a fourth mood representing the absence of unpleasant feeling ("I feel pretty good today;" "I'm not feeling nervous;" etc.),

Part A

Methods Employed (Continued): which we called "calm." The criteria for inclusion in the sample were:

1. The mood must occur in the immediate present: the patient must be jittery or gloomy at this moment in the interview, or angry directly with the therapist, not reporting such moods as having been felt in the remote or recent past.

2. Two modes of expression of the mood must be compatible: a pair of judges listened to the tape recording together, to judge compatibility of content and vocal expression. Instances in which the patient talked of being gloomy, but which "sounded" animated, angry, or whatever, were eliminated.

From this work a fifth mood evolved: the content was of anger, and yet the voice "sounded" hurt, complaining, whining, and the patient was weeping, compared with other instances of anger where the patient attacked the therapist from a position of equality or even of greater strength.

Four excerpts of each of these five moods were selected from a wide range of interviews, each excerpt being $1\frac{1}{2}$ minutes in length. This length was chosen on the basis of the maximum time any of the moods were sustained by the patient without perceptible shift. The 20 excerpts were then used as the basic data for two parallel studies, one of types of body movement associated with the different moods, and the other of judgment of mood from restricted cues.

Major Findings: Body Movement: Counts of gross movements of head and hands were made, and the frequencies subjected to simple analysis of variance. Frequency of head movements differentiated among the moods at the .01 level of confidence, while that of hand movements differentiated at the .001 level. Hand movements were then traced and measured both for distance of movement and for duration. Distance differentiated at the .001 level, but duration was unrelated to mood. Rate of movement, or distance/duration, differentiated at the .001 level.

As interesting as the individual results is the pattern of movements for the different moods. The frequencies of movement do not correlate with each other, but may lend themselves to profile analysis. The calm mood, for example, is characterized by the fewest head movements and the most frequent, but shortest hand movements. The angry mood, on the other hand, is characterized by the most frequent head movements, very few hand movements, but where they occur, hand movements cover the greatest distance. Rate of hand movement produces the same pattern as distance, and if it continues to do so in replication, will be discarded, since it is very time-consuming to determine.

Part A

Major Findings (Continued):

Judgment of Mood from Restricted Cues: Three judges were presented with the material in silent film form (eliminating content and vocal cues) and filtered tape (eliminating visual and content cues). Agreement among the judges was not high, but there was no systematic bias among the judges, and their judgments were pooled to test their success in identifying the moods. They could identify the angry excerpts from the filtered tape, because the patient talked loudly, and the hurt, complaining excerpts from the silent film, because the patient wept. But in general, the particular cues which were eliminated left the judges without enough information to go on, so that overall accuracy was low.

The method of presenting the material to the judges may have insured negative results for two reasons: 1. The judges had never seen, heard, or read any of the interviews with this patient, and so lacked a base-line on which to judge. Given some prior acquaintance with the patient's moods, they may have been able to identify these excerpts more accurately; 2. One combination of restricted cues was not tried for technical reasons, film with filtered sound. This combination would have eliminated only content. The circuitry for this condition is currently being arranged.

Scientific Significance to the Program of Mental Health Research: This is one of the methods being developed to use the data of filmed psychotherapeutic interviews for the study of the process of psychotherapy. Such an opportunity has not been available until facilities were constructed and interviews photographed. While the methods are being developed for the study of psychotherapy, it is our hope that they will have wider application.

Proposed Course of Project: Data have been collected for a replication of this experiment. While the levels of confidence represented in the results reported here are very high, there is still the possibility of chance fluctuations in samples of only four instances of each of the moods. While it is doubtful that the second sample will show no differences, if we are to use this technique for pattern analysis, we must be sure that the patterns will hold up in a wider variety of data. This study is, after all, not a test of an hypothesis, but rather is more like the construction of a psychometric instrument which will in turn be used to test hypotheses. We must, then, be thoroughly familiar with the parameters of the instrument so that we can rely on the final results.

Part B included No

Serial No. M-P-C-(C)-22
1. Laboratory of Psychology
2. Section of the Chief
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Parental Denial of Illness and its effect upon the subsequent health of their children.

Principal Investigator: Isabelle V. Kendig

Other Investigators: None

Cooperating Units: None

Man Years (calendar year 1960):		Patient Days (calendar year 1960):
Total:	0	0
Professional:	0	
Other:	0	

Project Description:

Objectives: To investigate to what extent, if any, parental beliefs which negate disease and foster positive attitudes to health, when inculcated in early childhood, are effective in promoting the health of their offspring in adult life.

Methods Employed: It is planned to compare the health records of groups of college students and of military personnel with controls equated except for the variable that the experimental groups will have been brought up to deny the reality of illness and to assume positive attitudes to health. The case material has already been selected for this study. The names of all male Principia graduates, 1939-1942, the majority of whom may be expected to have been in the Military Service during World War II were obtained to constitute the major experimental group. They number 148. A pool of 300 names, randomly selected, of Harvard men graduating in the same 4-year period was also developed on which to draw for matched controls. As a sub-group to be studied, the names of 25 Christian Science Chaplains were also obtained. It is planned to match these with comparable groups of Protestant, Catholic and Jewish Chaplains whose names are available in the Army Register. Another sub-study, already initiated, involves the review of the health records of 30 Christian Scientists from the student body currently at Harvard for comparison with matched controls who are not of their faith. It has been hoped that the major official objection to the prosecution

Part A

Methods Employed (Continued): of this research was removed with the procurement from the Mother Church in July, 1959, of a letter giving unqualified approval of the project.

Patient Material: None.

Major Findings: There are none to report at this time as the study has never really gotten under way since, although 16 months have passed and all conditions supposedly have been met, official approval has not yet been obtained.

Scientific Significance of the Program to Mental Health Research: At a time when attention is shifting from an exclusive preoccupation with pathology to studies of positive health, an investigation of parental attitudes and beliefs which may play a role in promoting it should be contributory.

Proposed Course of Project: Granted access to Military health records, the plan is to extract the pertinent data and utilize small group statistics in the comparison of the samples selected.

Part B included No

Serial No. M-P-C-(C)-23
1. Laboratory of Psychology
2. Section of the Chief
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: An experiment in psychotherapy.

Principal Investigator: Paul Bergman

Other Investigators: William C. Jenkins, Charmian Elkes, Irene Waskow

Cooperating Units: None

Man Years (calendar year 1960):		Patient Days (calendar year 1960):
Total:	.50	10
Professional:	.50	
Other:	0	

Project Description:

Objectives: (A) To formulate testable hypotheses about the basic processes involved in psychotherapy.

(B) To submit such hypotheses to preliminary clinical tests in order to eliminate any that have little promise of validity or testability.

(C) To select one or two hypotheses of promise and to submit them to experimental tests under controlled conditions.

Methods Employed: Objective (A) was achieved by a study of the literature and "arm chair speculation." Objective (B) was approached by clinical testing, including essentially gathering of impressions from courses of psychotherapy with a few well-selected patients. Objective (C) was to be approached after achievement of (A) and (B).

Major Findings: The hypotheses tested seemed to lead to rapid symptomatic improvement, but not to optimal development of the patients' personalities. It was concluded that the formulations about the basic processes involved in psychotherapy were inadequate.

Scientific Significance of the Program to Mental Health Research: The refutation of the held hypotheses was helpful since it led to

Part A

Scientific Significance of the Program to Mental Health Research (Cont.): other hypotheses which will be tested in a new project.

Proposed Course of Project: The project has been terminated.

Part B included No

Serial No. M-P-C-(C)-24
1. Laboratory of Psychology
2. Section of the Chief
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: The Effects of Various Amines on Psychophysiological Responsivity and Reaction Time of Schizophrenic Patients.

Principal Investigator: Theodore P. Zahn

Other Investigators: David Rosenthal

Cooperating Units: Clinical Sciences Laboratory

Man Years (calendar year 1960):
Total: .50
Professional: .25
Other: .25

Patient Days (calendar year 1960)
96

Project Description:

Objectives: To determine the effects of marsilid and of several precursors of serotonin on autonomic activity of schizophrenic patients and on the ability of these patients to maintain a preparatory set.

Methods Employed: Two types of behavioral studies were carried out: (1) GSR and heart rate were recorded continuously during repeated presentations of a light and a tone which were presented alternately for a series of 20 trials. (2) Reaction time was measured using short and long constant preparatory intervals.

Throughout the experiment some patients were continuously receiving marsilid and some were not. The amines were administered according to a complex double-blind plan in which the order of administration was usually counterbalanced. The amines investigated were histidine, tryptophan, phenylalanine, methionine, tyrosine and glutamine.

Patient Material: Eleven schizophrenic patients from Ward 2-West.

Major Findings: Phenylalanine produced a marked and significant decrease in basal skin resistance in seven of ten patients in comparison to tryptophan and tyrosine. A second administration under a higher level of marsilid produced results in the same direction but less striking. No other general and consistent effects of the amines

Part A

Major Findings (Continued): were found despite some striking behavioral changes noted on the ward. However, in only a few instances were these behavioral changes present to any marked degree during our testing.

Scientific Significance to the Program of Mental Health Research: The negative findings involving the precursors to serotonin studied here suggest that whatever effects they may have on behavior are not due to a generally high level of autonomic arousal. The positive finding with regard to phenylalanine may have some implications in the physiology of the GSR, especially so since phenylalanine seems to be involved in the metabolism of epinephime.

Proposed Course of Project: No further studies planned at present.

Part B included No

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B. Honors, Awards and Publications

Publications Not Directly Related to this Project:

Zahn, T. P.: Size estimation of pictures associated with success and failure as a function of manifest anxiety. J. Abnorm. Soc. Psychol. (In Press).

Serial No. M-P-C-(C)-26
1. Laboratory of Psychology
2. Section of the Chief
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Index of psychoanalytic interviews of a patient.

Principal Investigator: Allen T. Dittmann

Other Investigators: None

Man Years (calendar year 1960):		Patient Days (calendar year 1960):
Total:	.7	0
Professional:	.2	
Other:	.5	

Project Description:

Objectives: The purpose of the index is to make more available for research the vast information contained in the recordings and motion pictures of the psychoanalysis currently being conducted (see "An analysis of the psychotherapeutic process, particularly the psychoanalytic process," Office of the Director, Clinical Investigations). While it is obviously impossible to forecast all of the possible studies to which these data may be submitted, certain areas of the interviews, such as the topics covered, will undoubtedly be the focus of many studies, and can be listed as to the times of their occurrence in the interviews. Thus an investigator wishing to refer to certain topics or combination of topics will be able to find them in film, tape, and typescript.

Methods Employed: The index will contain four categories to begin with: Topic, Affect, Time Referent, and Person Referent. Topic is defined as superficially as possible, the topic of conversation. The chief aim of this work is to standardize on a level of abstraction which will be low enough to maintain reliability of coding and to permit combining categories for maximum flexibility in information retrieval.

The Affect category is simply a list of all affect words used in the interview -- "happy," "nervous," and the like -- with no inference from the coder. The Time Referent category is the time referred to in the topic -- childhood, the immediate present of the interview, day-to-day events in the current life of the patient. The Person Referent category is the people in the patient's life referred to in the topic.

Part A

Methods Employed (Continued): All of the categories are collated to page numbers of the typescript of the interview, which in our format average slightly under one minute in length.

Major Findings: Indexing an interview by these methods requires about 6 hours of time. We have indexed over 60 interviews, delineated 84 topics, and 9 time referent categories. Investigators have indexed several interviews independently, and agreement on topic change is very high, with agreement on topic category more variable from interview to interview. This work has led to refinements of categories, and further checks on inter-coder agreement are in progress.

Scientific Significance to the Program of Mental Health Research: See Objectives.

Proposed Course of Project: In addition to the methods outlined above we are beginning to explore electronic data storage and retrieval methods of indexing. These methods will not be able to do the complete job from the beginning (from the typing of the interview), but may be a useful adjunct in some areas. This work is at the very beginning stage at the time of this report.

Part B included No

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B. Honors, Awards and Publications

Publications Not Directly Related to this Project:

Dittmann, A. T.: The need for ongoing research in the general function of the orthopsychiatric team. Amer. J. Orthopsychiat. 30: 79-86, 1960.

Goodrich, D. W., and Dittmann, A. T.: Observing interactional behavior in residential treatment. A.M.A. Arch. Gen. Psychiat. 2: 421-428, 1960. (This publication is related to closed Project No. M-P-C-(C)-6.)

Raush, H. L., Dittmann, A. T., and Taylor, T. J.: Person, setting, and change in social interaction. Hum. Rel. 12: 361-378, 1959.

Serial No. M-P-C-(C)-27
1. Laboratory of Psychology
2. Section of the Chief
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: An Empirical Investigation of "Mental Health."

Principal Investigator: Paul Bergman

Other Investigators: Charmian Elkes, William C. Jenkins, Irene Waskow

Cooperating Units: None

Man Years (calendar year 1960):

Total:	.10
Professional:	.10
Other:	.0

Patient Days (calendar year 1960): 0

Project Description:

Objectives: (A) To empirically investigate the higher ranges of mental health by a variety of methods.

(B) To examine in this area the adequacy of some concepts at present available, for instance, the "fully functioning personality", the "mature personality", the "sense of integrity", "freedom from anxiety", "absence of self-consciousness", "self-realization", "individuation".

(C) To gain knowledge about directions and limits of personality growth and their relation to givens of constitution and experience.

Methods Employed: The plan is to begin by taking a few relatively healthy subjects into psychotherapy, and continuing the therapy far beyond the point at which one usually tends to stop, namely when comfort and efficiency of functioning seem achieved. Clinical observations and experimental tests appropriate to the hypotheses investigated will be used on these subjects. Other methods will be considered as soon as the fruitfulness of this research is felt to be more than a distant hope.

Part A (Con'd.)

Major Findings: None so far. The project is in the phase of initial planning.

Scientific Significance of the Program to Mental Health Research: While empirical knowledge of mental illness has been growing for nearly a century, mental health has remained practically unknown territory. It would be important to know, for instance, whether what we nowadays consider the average healthy adjustment of adults comes or does not come close to the limit of such people's potentialities. The fields of philosophy, religion, education are not less concerned than psychology and psychiatry with the problems which the present research attempts to clarify.

Proposed Course of Project: After review of the yield of the first investigations it will be possible to gauge the direction and extent of future work. If, for instance, no new phenomena worth knowing have come under observation and the impression prevails that further work would not yield more interesting results, the project would be turned into different directions or closed. In the opposite case, however, the project would expand to chart a large and important unknown territory.

Part B included No

Serial No. M-P-C-(C)-28.
1. Laboratory of Psychology
2. Section of the Chief
3. Bethesda

PHS--NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: The Influence of Freud on Psychology

Principal Investigator: Dr. David Shakow

Other Investigators: Dr. David Rapaport, Austen Riggs Center, Inc.

Cooperating Units: None

Man Years:
Total: .44
Professional: .10
Other: .34

Patient Days: None

Project Description:

Objectives: To evaluate the impact of Freud's theories on academic psychology.

Methods Employed: Historical and scholarly analysis.

Patient Material: None.

Major Findings: (1) Delineation of milieu in which Freud's thinking arose, (2) Analysis of the influences on Freud, (3) Historical survey of the explicit implicit influences of various major Freudian theories on the psychology of this century to the present day.

Scientific Significance of the Program to Mental Health Research: Historical works of this kind help to organize a field as well as to clarify areas of theoretical confusion. It serves also to point up areas for further development.

Part B included: No.

Serial No. M-P-D(C)-1
1. Laboratory of Psychology
2. Section on Child Development
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: The Preparation of Procedures for Observing and Recording Infant Behaviors and Mother-Child Interactions in Testing Situations for Use in a Study of Infant Development. A Pilot Study.

Principal Investigator: Nancy Bayley

Other Investigators: None

Cooperating Units: None

Man Years (calendar year 1960):

Total:	1.00
Professional:	.33
Other:	.67

Patient Days:
None

Project Description:

Objectives: To devise and pretest a set of tests and methods of appraising and recording mother and child behaviors in a situation in which infants are given developmental tests. The further objective is preparation for initiating a longitudinal study of intellectual and personality development of children from early infancy.

Methods Employed: During the past two years infants with their mothers have been brought into the Admission and Follow-Up Department of the Clinical Center for periods of an hour.

A series of revisions of the various test forms and rating scales was tried out at these sessions, until satisfactory forms were developed. A "longitudinal" group was gradually built up of some 30 infants who have been brought in at three- to six-month intervals for retests.

Major Findings: The instruments developed in this project will be used as research tools in a new longitudinal study, the purpose for which they were devised.

Scientific Significance to the Program of Mental Health Research: Earlier longitudinal studies of the development of infants and children have yielded very important leads on the early determiners of personality and of factors that influence mental health. However,

Part A

Scientific Significance to the Program of Mental Health Research (Continued): these earlier findings are only suggestive and new studies should be made with more carefully designed methods of observation and recording of the kinds of data that now appear to be most pertinent.

Proposed Course of Project: This project has served its purpose and is essentially completed. The longitudinal study will be carried on as a new project.

Part B included No

Serial No. M-P-D(C)-2
1. Laboratory of Psychology
2. Section on Child Development
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Standardization of Infant Scales of Mental and Motor Development.

Principal Investigator: Nancy Bayley

Other Investigators: Marjorie P. Honzik, University of California.

Cooperating Units: National Institute of Neurological Diseases and Blindness.

Man Years (calendar year 1960):		Patient Days:
Total:	1.00	186
Professional:	.33	
Other:	.67	

Project Description:

Objectives: To revise and restandardize the California First Year Mental Scale to be extended through two years and renamed an Infant Scale of Mental Development, and also the California Infant Scale of Motor Development, to be renamed An Infant and Preschool Scale of Motor Development. The revisions of the scales are designed to fill a serious gap in the current status of developmental tests for infants. The infant scales now in use in this country were all standardized on data obtained 20 to 30 years ago on small samples of infants usually from a geographically, culturally and often socio-economically restricted source. Because of these inadequacies of sampling, we have no assurance that the age norms in any of them are representative of infants in the country generally. The revisions are being standardized by testing representative samples from a variety of geographical areas, as well as special groups of specified ethnic or pathological classes.

Aside from the sampling, however, current theories about the nature of the developmental processes call for inclusion in the scales of a wider range of behaviors in order to render the evaluations of a child's status more meaningful.

Methods Employed: The original scales have been gone over item by item to make the procedural directions more clear; new items were

Part A

Methods Employed (Continued): added for trial; new record forms and work sheets were developed that both increase the ease of administering and recording and also allow for fuller descriptions of the infants' responses. An additional form was devised for recording the child's emotional, attitudinal, energy-output and goal-directed behaviors. These latter are being analyzed for age and developmental trends and for the relation of individual differences to scores of mental and motor functioning. A revised set of test materials includes specifically made plastic form boards, boxes and other items. These were tried out on small samples of infants and further revisions then made. A program of testing was carried out in cooperation with NINDB, whose Collaborative Project is using the scales. Each of ten of the projects furnished tests on approximately 120 infants aged one through 15 months. These tests have been completed and are partially analyzed. In addition, infants from geographical areas and types of populations not sampled in these ten groups are being tested.

A series of tests for estimating item reliability were made on both a test-retest and a tester-observer comparison. On the basis of these findings and other tests of item adequacy, unreliable and otherwise inadequate items have been dropped from the scale. New age-placements have been determined for the remaining items and these have been rearranged in the new order of difficulty. Analyses are now in progress on differences between groups such as Negroes, Whites, Puerto Ricans, and children from different social class groups, for individual items and for total scores. On the basis of these findings it will be determined what additional samples of babies should be tested. The NINDB projects are now giving the tests to eight-month-old infants, with a program to test 50,000 at this age in the next five years. Norms will be set up so that a child can be given a score relative to his age (a standard score or an I.Q. equivalent), for each total scale (mental, motor) and possibly for any valid sub-scales. Age norms will also be established for the Infant Behavior Profile, together with an appropriate method for evaluating and interpreting it.

Major Findings: In general, the babies in our present standardization samples are more advanced than the babies of the original standardization 30 years ago. A new record form has been devised and the directions for administration of items have been clarified and simplified. Item analyses show good reliability, and item validity. The tests in this new form are being used by the NINDB Collaborative Projects, and are proving satisfactory.

Part A

Scientific Significance to the Program of Mental Health Research: There is need for really good, objectively-scorable, well-standardized tests of developmental functioning in infants that covers the age span between birth and two years. This is of primary importance to basic research that is directed toward early detection of such conditions as mental deficiency and emotional disturbances. A good test will also function as a basic tool in studies of learning in infants, of the effects of environmental deprivation and emotional trauma on the infant's development and personality adjustment.

Proposed Course of Project: The Infant Behavior Profile will be analyzed, and a revised form developed for it. The standardization tests will be re-scored on all three of the new forms (Mental, Motor and Behavior Profile). Means and SD's of scores for various sub-samples of babies will be computed and compared. An analysis will be made of the standardization sample to date, in respect to such factors as socioeconomic status, ethnic groups, sex, and geographical location. On the basis of needs revealed by this analysis additional samples will be sought and tested for improving the norms. When adequate tests have been made and the data appropriately analyzed a final set of forms, directions and scoring standards will be prepared. At a later time the tests will be given to samples of children aged 16 to 30 months and these will be analyzed by similar procedures.

It is important that these tests (including a kit of test objects, record forms and book of directions) then be made available, with appropriate controls, to persons and institutions who are qualified to use them in accordance with the code of ethics of the American Psychological Association. In this respect Government regulations are in conflict with professional ethics which require that distribution and use of psychological tests be limited to those who are properly trained and qualified. As each kit contains about 35 items which have been carefully selected or specifically designed and manufactured to order, the Government does not have any facility for assembling the kits for distribution. It would be most appropriate if an ethical private firm which handles psychological tests and instruments could be given rights, by contract with the principal investigator, to publish and distribute the kits, directions and record forms. Such firms have standard procedures for handling these materials. Some resolution of this problem will be necessary if the tests are to have the generally useful function for which they are designed.

Part B included No

Serial No. M-P-D(C)-4
1. Laboratory of Psychology
2. Section on Child Development
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Longitudinal Studies of the Relationship of Maternal Behavior to the Subsequent Social, Emotional, and Intellectual Development of Children.

Principal Investigators: Nancy Bayley and Earl S. Schaefer

Other Investigators: None

Cooperating Units: None

Man Years (calendar year 1960):

Total:	1.41
Professional:	.74
Other:	.67

Patient Days:
None

Project Description:

Objectives: The objectives of this project are to study by means of the available data of the Berkeley Growth Study (54 cases), the long term interrelationships between maternal behavior and child behavior, emotional, attitudinal and intellectual. Previous researches in this Section have developed a method of quantifying the maternal behaviors, and of organizing it into a meaningful conceptual framework. Using similar concepts, the child behaviors have also been organized for purposes of mother-child comparisons.

Methods Employed: Data in the records of the Berkeley Growth Study included both descriptive notes and ratings on mothers and children, made at the times they were seen between the children's ages of birth to 21 years. The notes on the mothers cover observations made during the children's first three years, and one to three home interviews when the children were nine to 14 years. Ratings on the children were made at the times of testing sessions at 40 ages, one month through 12 years; and descriptive notes were written at the times of 12 testing ages between 12 and 18 years.

The original ratings on the children were combined in two different ways: to improve reliability by adding scores for two or three adjacent ages, and to obtain general behavior trait scores

Part A

Methods Employed (Continued): within an age level by combining several correlated ratings.

The descriptive notes on the children's adolescent behaviors were rated on a set of 96 adjectives that had been selected according to a conceptual model of personality variables. These adjective ratings were intercorrelated and were found to fit the conceptual model.

The method has been further to intercorrelate for the boys and girls separately, all of the maternal ratings, child ratings, children's intelligence scores and a set of available socioeconomic variables. These have been organized in several ways, for maternal consistency and child consistency in behavior; relations of socioeconomic variables to behavior; maternal behavior-child behavior interrelations; and relation of children's intelligence to both maternal and child behavior ratings.

Major Findings: Both maternal and child behaviors could be organized into meaningful circumplex orders of neighboring for all sets of data and all ages. Maternal behavior was found to be fairly consistent in the love-hostility dimension (r = .68), but not in the dimension of autonomy-control. Maternal behavior was somewhat related to socioeconomic status, more so in the mothers of boys than of girls: the more loving, accepting tending to be of the higher socioeconomic status. Children's behaviors show little consistency over the 18-year span but are fairly consistent in the period of latency, with rapid changes occurring in infancy and to some extent in adolescence. There is some evidence that relative activity in infants is related to impulsivity and uncontrolled extraverted behavior later. Emotional adjustment during the first two years does not seem to be predictive of later overt manifestations of adjustment.

The boys' behaviors show a consistent pattern of relations to their mothers' behaviors, the early maternal behavior continuing to exhibit the same pattern through 12 years. The later maternal behavior shows a similar pattern of correlation with both the sons' current and earlier behaviors. The mother-daughter correlations are different: the daughters' behaviors having a strong pattern of correlation with concurrent maternal behavior, but little relation to the more distant maternal behaviors. That is, the girls' behaviors after three years show diminishing relation to early maternal scores, while the maternal ratings at the child's early adolescence show little relation to their daughters' behavior in infancy and early childhood.

Part A

Major Findings (Continued):

Relations between child's intelligence and the behavioral ratings are not yet analyzed. Preliminary inspection indicates some consistent age-trends in changing relations of intelligence to both maternal and child behaviors.

Scientific Significance to the Program of Mental Health Research: The results of this study are particularly relevant to the currently influential theories of Sullivan, Fromm, and Horney. Since most theories of maternal influence upon personality development have been developed from clinical and retrospective studies, tests of these theories by predictions from longitudinal data are valuable in evaluating these theories. The unique data on mothers from observation and interview at two different ages, and the unique longitudinal data on personality development will add substantially to the body of knowledge on social influence upon personality development. The results of the study will be relevant to many fields of personality research on social class, maternal behavior, intellectual development, and social and emotional development.

Proposed Course of Project: Several papers have been completed and published on the maternal data. These cover the development of the maternal behavior scoring system, the consistency of maternal behavior, and the relation of maternal behavior to socioeconomic variables. It is proposed to publish the data on child behaviors and mother-child relations in two monographs. One of these "Maternal Behavior, Child Behavior and Their Intercorrelations from Infancy to Adolescence" should be ready to submit for publication within the next month. The second, "Correlation of Maternal and Child Behaviors with Intelligence, Birth to Eighteen Years," will be prepared within the next six months.

Part B included Yes

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B

Publications other than abstracts from this project:

Bayley, Nancy, and Schaefer, E. S.: Relationships between socio-economic variables and the behavior of mothers toward young children. J. Genet. Psychol. 96: 61-77, 1960.

Schaefer, E. S., and Bayley, Nancy: Consistency of maternal behavior from infancy to preadolescence. J. Abnorm. Soc. Psychol. 61: 1-6, 1960.

Bayley, Nancy, and Schaefer, E. S. Maternal behavior and personality development: data from the Berkeley Growth Study. In: Proceedings of the Regional Research Council on Child Development and Child Psychiatry. (Accepted for publication)

Serial No. M-P-D(C)-5
1. Laboratory of Psychology
2. Section on Child Development
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Development of a Theoretical Model for the Relationship of Parental Behavior to Personality Development.

Principal Investigators: Earl S. Schaefer

Other Investigators: None

Cooperating Units: None

Man Years (calendar year 1960):
Total: .40
Professional: .30
Other: .10

Patient Days:
None

Project Description:

Objectives: The purpose of this project is to develop conceptual models that will contribute to the understanding of the relationship of parental behavior to social and emotional development of the child. These models would also be useful in planning future research on parental influence on personality development.

Methods Employed: The models for maternal behavior, child behavior, and their interrelationships have been developed from generalizations of empirical organizations of statistical data. Each set of data was ordered by Guttman's radex method, i.e., by organizing variables into sequential orderings according to the proportion of shared variance. Organizations of several sets of empirical data for both maternal behavior and child behavior were very similar to one another, and therefore could be generalized into conceptual models.

Major Findings: The conceptual model for parental behavior is organized within two major dimensions of Love versus Hostility and Autonomy versus Control. This model has been confirmed from inventory measures of parental attitudes, from ratings of maternal behavior, and from the child's report of parental behavior. The model for social and emotional behavior has been organized within the two dimensions of Love versus Hostility and Extraversion versus Introversion. This model has been confirmed from several sets of rating data and from several

Part A

Major Findings (Continued): objective inventories. Hypotheses about the relationship of the parental behavior model to the child behavior model have been supported by a study of the interrelationship of maternal behavior and child behavior reported in project M-P-D(C)-4.

Scientific Significance to the Program of Mental Health Research: Although many theories of personality development stress the importance of the parent-child relationship, little consensus has been achieved on the relationship of specific patterns of parent behavior to specific patterns of child behavior. The models for maternal behavior and for child behavior have increased understanding of both of these sets of behavior. This project has also developed a researchable hypothesis of the relationships between maternal behavior and the social and emotional development of the child.

Proposed Course of Project: Further work may be done on the model for social and emotional behavior. Organizations of objective personality inventory data and of behavior rating data that provide the empirical basis of the model may be published.

Part B included Yes

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B

Publications other than abstracts from this project:

Schaefer, E. S.: Converging conceptual models for maternal behavior and for child behavior. In Glidewell, J. C. (ed.): Parental Attitudes and Child Behavior. Springfield, Charles C. Thomas, 1960. (In press)

Schaefer, E. S.: Converging conceptual models for maternal behavior and for child behavior. In: Proceedings of the International Congress of Psychology. (Accepted for publication)

Publications Not Directly Related to This Project:

Schaefer, E. S., and Bell, R. Q.: Development of a parental attitude research instrument. Americana. 5: 29-51, 1959. (This publication is related to a project which was completed in 1955.)

Serial No. M-P-D(C)-8
1. Laboratory of Psychology
2. Section on Child Development
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: The Reinforcing Effects of Environmental Stimuli for Infant Behavior: The Beginnings of an Analysis of the Behavioral Consequences for the Infant of Environmental Conditions Provided by Caretaking.

Principal Investigator: Jacob L. Gewirtz

Other Investigators: None

Cooperating Units: None

This project is held in abeyance. Dr. Gewirtz is on leave of absence as Visiting Professor of Psychology at the Hebrew University, Jerusalem, Israel.

Part B included Yes

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B

Publications Not Directly Related to This Project:

Gewirtz, J. L.: A learning analysis of the effects of normal stimulation, privation and deprivation on the acquisition of social motivation and attachments. In: Proceedings of the Conference on Mother-Infant Interaction and Its Relation to Mental Health. (Accepted for publication) (This publication is related to completed project M-P-D(C)-24.)

Serial No. M-P-D(C)-22
1. Laboratory of Psychology
2. Section on Child Development
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: The Shaping of the Infant's Social and Exploratory Behavior by the Environment.

Principal Investigator: Harriet L. Rheingold

Other Investigators: None

Cooperating Units: None

Man Years (calendar year 1960):		Patient Days:
Total:	2.33	None
Professional:	1.00	
Other:	1.33	

Project Description:

Objectives: The main purpose of this program is to investigate the process by which the human infant's response to social and non-social objects is modified by environmental events, both social and non-social, contingent upon his exploratory activities. We are dealing, then, with behavior which differs from those usually considered to be under the control of the homeostatic drives. It is behavior which can be characterized as adaptive, and is similar to, if not identical with, behavior which in the older organism is labeled as sociability, curiosity, manipulatory drive, and play.

The research program is guided by the following hypothesis: first, that in the beginning the infant's responses to people and to things are similar and, second, that differentiation of response occurs by a process of learning based on the different nature of the responses given the infant's own overtures by social and non-social objects.

To gain an understanding of the process it is necessary to discover the environmental stimuli that arouse behavior in the infant and those that, in turn, reinforce behavior. For the present, the stimulus dimensions to which attention is being directed are novelty, familiarity, and complexity, both spatial and temporal. Research will be designed to determine whether, and under what circumstances, the novel, the familiar, and the complex arouse

Part A

Objectives (Continued): certain infant behavior and also reinforce these behaviors.

Maternal care continues to be an important part of this program; although at the present time it is not being formally investigated, it is always implicit in our thinking. Maternal care is conceived of as the major source of environmental stimulation for the infant; it is the caretaker who provides both the evoking and the reinforcing stimuli.

Implicit also in the program is an interest in a comparative study of social and exploratory behavior in other mammals. Such comparative behavioral research merits study in its own right but especially because it throws into prominence those qualities which are uniquely human. For the same reason a study of maternal care in other mammals is also a matter of concern.

Methods Employed: Three methods have been employed, each depending upon the stage of the problem under study and its suitability for the questions being asked. The first is naturalistic observation of infants and mothers (or caretakers) in their usual environments, often with controls imposed upon the times when the observations are made and upon the behaviors which are to be observed. In this area particular attention has been paid to sequences of interaction between mother and child. What is an infant's response to an act of the mother's, what a mother's responses to an act of her infant's?

In the second method of investigation these naturally-occurring sequences of behavior are reproduced under controlled conditions but still in the infant's usual environment. Such a method was employed in the conditioning study of the infant's vocalizations.

The third method, which is now being perfected, seeks still further to control the presentation of the stimuli (which result from the infant's own behavior) and the recording of the infant's response. For greater precision required by this method laboratory space and instrumentation are necessary.

Major Findings: 1. Observation has revealed the considerable amount of time and energy spent by the young infant in seeking a response from his environment, more from certain objects than from others.

2. Measures of the responses to people (the experimenter) and to things (rattles) of three-month-old infants receiving different amounts of environmental stimulation revealed few differences.

Part A

Major Findings (Continued): What differences did appear showed that infants receiving less day-by-day stimulation responded more quickly and more fully.

3. The discovery that some non-social objects were effective in producing the smiles and vocalizations usually associated with the response to social objects suggested the hypothesis that the origins of the smiling response may be based on the stimulus properties of the object itself and not on a history of need-reduction.

4. Pilot studies with three- and four-month-old infants indicate that panel-pressing may function as a free operant and that illumination of these panels when made contingent upon the infant's press may function as a reinforcer. Interestingly enough, even two-month-old infants will spontaneously exert pressure on panels without any "shaping" of the behavior.

5. The data gathered at Jackson Memorial Laboratory on maternal care in the dog is in process of analysis. They should yield answers to such questions as: What are the caretaking operations performed by the mother? How do they change as the infants mature? What behavior of the infant pup stimulates a caretaking response on the part of the mother?

Scientific Significance to the Program of Mental Health Research: The response given by the young human infant to objects in his environment are seen as some of the earliest evidences of creativity and sociability, traits important in the behavior of man and valued by our culture. Further, the infant's responses are easily modifiable by experience, much of which comes to him at his mother's hand. Thus, any knowledge gained about the dimensions of these experiences should be of considerable significance for the welfare of the individual and of the group. If it is true, as I suspect, that an interest in people develops out of an interest in any number of objects, not all of them social, work in this area might be of considerable theoretical importance. The apparently primary nature of this responsiveness and its modifiability by environmental events of a stimulating nature may make necessary some revision of currently accepted theory about the development of social behavior and object attachment.

Proposed Course of Study: The first step is to study the effects on exploratory behavior in the infant of different stimulus contingencies resulting from these responses; that is, to find out which stimuli reinforce exploratory responses and then to determine the properties on which their reinforcing depends. This aim involves

Part A

Proposed Course of Study (Continued): verifying that the consequent stimuli have a lasting strengthening effect on these responses, and that this effect depends upon the consequent stimuli's closely following the response.

In the first step, novelty, familiarity, and spatial and temporal complexity will be investigated. All of these stimulus properties have in common the characteristic that they are themselves a joint function of the infant's past experience and the physical attributes of the stimuli; they are not the physical attributes alone.

It is planned, further, to study the development of these aspects of exploratory behavior over a range of several months, probably from the third through the twelfth month.

The later steps of the research program will investigate the relationship between exploratory behavior and other kinds of behavior in the infant--specifically, social and emotional behavior, and intellectual development.

The questions asked by this project require apparatus which will deliver a response (lights of varying or changing colors will be the first class of stimuli to be employed) and record the infant's responses automatically (here, presses of a panel which lights up). The construction of the apparatus took nine months from the date of request and then proved to be faulty. It is clear now, also, that not only will adequate laboratory space be required to carry out the project, but also an unbiassed population of normal infants. It may be wasteful to continue work at St. Ann's which provides neither adequate working space nor an unbiassed sample. Still, the institution may be useful for the rapid screening of new techniques.

It is our hope, further, to explore the possibility of studying the psychophysiological correlates of exploratory behavior, e.g., certain electro-oculographic, electromyographic and electro-encephalographic measures, for which adequate laboratory space at NIH would be necessary.

Part B included Yes

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B

Publications other than abstracts from this project:

Rheingold, Harriet L.: The measurement of maternal care. Child Develpm. 31: 565-575, 1960.

Rheingold, Harriet L.: The effect of environmental stimulation upon social and exploratory behavior in the human infant. In: Proceedings of the Conference on Mother-Infant Interaction and Its Relation to Mental Health. (Accepted for publication)

Serial No. M-P-D(C)-23
1. Laboratory of Psychology
2. Section on Child Development
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Development of Methods for the Study of Maternal Personality and Behavior Variables.

Principal Investigator: Earl S. Schaefer

Other Investigators: None

Cooperating Units: National Institute of Neurological Diseases and Blindness, Walter Reed Army Hospital

Man Years (calendar year 1960):

Total:	.50
Professional:	.00
Other:	.50

Patient Days:
None

Project Description:

Objectives: The goal of this research has been to develop methods for the study of maternal adjustment and behavior during the perinatal period. The study was originally motivated by the need for such methods for use in the Collaborative Project of NINDB. Recent studies have suggested that maternal adjustment during pregnancy may affect the behavior and development of her child. The immediate postnatal period is also a critical period for the development of the mother-child relationship. Development of efficient methods for the psychological evaluation of pregnant women and for assessing maternal adjustment to the postnatal period would provide tools for the further investigation of maternal influence upon child development.

Methods Employed: Two objective inventories, a Pregnancy Research Inventory and a Postnatal Research Inventory, have been developed from a search of the literature on the perinatal adjustment of mothers. Both inventories investigate psychosomatic symptoms of the mother and her psychological response to her current situation.

In this project an attempt was made to obtain from obstetricians ratings of response to labor and delivery. Preliminary analysis of these ratings suggests that without training of the raters the ratings are too unreliable to be useful in research.

Part A

Methods Employed (Continued):

The rating scales for describing the behavior of the mother with her infant during a psychological examination are currently being used by the NINDB Collaborative Project in a modified form. No further investigation of these rating scales is planned by this laboratory in view of the continuation of that phase of this project by the NINDB Collaborative Project.

Major Findings: Analysis of the Pregnancy Research Inventory reveals three major patterns of response: 1. Dependency, Fears for Baby and Fears for Self; 2. Depression, Irritability, and Lack of Desire for Pregnancy; and 3. Numerous psychosomatic symptoms before pregnancy, during pregnancy, at menstruation, and at times of emotional stress. These patterns are reliably measured by the inventory.

The Postnatal Research Inventory also reveals three patterns of response: 1. Fear or Concern for the Baby, Need for Reassurance, and Intrapunitiveness; 2. Perceives Negative Aspects of Childrearing, Irritability, Depression, and Extrapunitiveness; and 3. Psychosomatic symptoms. Significant differences were found between primiparae and multiparae for the first cluster on both inventories. Significant correlations between the pregnancy data and postnatal data were found for a sample who had been tested with both inventories. These results suggest that the scales are sensitive to differences between groups and that the scales are tapping relatively consistent dimensions of maternal behavior. The results appear to justify further studies using these scales.

Scientific Significance to the Program of Mental Health Research: Recent studies of both animals and humans indicate that anxiety and stress during pregnancy may be related to the physical, mental and emotional development of the offspring. Methods are needed to investigate these leads further on larger clinical populations. Methods are also needed to study mother-child interaction immediately after birth. The inventories developed here have already been adopted by several investigators prior to their publication. They may give us further insight into the importance of psychological adjustment of the mother to the development of the child.

Part A

Proposed Course of Project: An adaptation of the Pregnancy Research Inventory is currently being pretested by the staff of the Collaborative Project, NINDB. This laboratory is also relating the pregnancy inventory to the course of labor and delivery in order to check the predictive validity of the scales. After further investigation the scales will be published to make them readily available to others.

Part B included No

Serial No. M-P-D(C)-25
1. Laboratory of Psychology
2. Section on Child Development
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Demonstration of the Infant Scales of Mental and Motor Development: A Sound Motion Picture.

Principal Investigator: Nancy Bayley

Other Investigators: None

Cooperating Units: None

Man Years (calendar year 1960):
Total: .37
Professional: .00
Other: .37

Patient Days:
None

Project Description:

Objectives: To present testing procedures and characteristic responses to the tests of infants aged one through 15 months, with explanatory commentary. The purpose is to provide a demonstration device for illustrating the infant scales, to be used in training and refreshing psychologists in the use of the tests and the evaluation of developmental aspects of infant responses to the test procedure.

Methods Employed: Sound motion pictures with simultaneous tape recordings have been made on normal, healthy infants at each month of age, one through 15 months. These films are now being studied and representative segments are being selected so that the entire range of the scales will be covered with characteristic variations in responses represented. Exploratory comments will be dubbed in at relevant places, and the whole will be organized into one or several films.

The films have also been studied carefully as aids to the standardization of the developmental scales to determine more accurate criteria for scoring specific behaviors on the various test items.

Major Findings: The pictures have now been made and the analysis started, but no major findings are yet available.

Part A

Scientific Significance to the Program of Mental Health Research: This illustrative film will be of great value as a training device and as a base of reference of normal behavior for psychologists, pediatricians and others concerned with evaluating the development of infants. Deviant behavior in intellectual functions, motor coordinations and emotional-personality variables of infants need to be interpreted in relation to their age-norms.

Proposed Course of Project: It is planned to continue the analysis and editing of the films during the calendar year 1961. Once the master film is complete it will be made appropriately available for use by qualified scientists.

Part B included No

Serial No. M-P-D(C)-26
1. Laboratory of Psychology
2. Section on Child Development
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: An Investigation of the Child's Perception of Parent Behavior.

Principal Investigator: Earl S. Schaefer

Other Investigators: None

Cooperating Units: None

Man Years (calendar year 1960):
Total: .70
Professional: .30
Other: .40

Patient Days:
None

Project Description:

Objectives: The purpose of this project is to develop a method of assessing the child's perception of parent behavior and to determine the interrelationships of various components of parent behavior as perceived by the child. The results of this approach to parent behavior will be compared with results obtained from parent behavior ratings and from parental attitude inventories. If the child's report could be demonstrated to be highly related to observations, an economical way of obtaining information on parent behavior would be provided. If the child's report is not highly related to the observed behavior of the parent, the data would still increase understanding of the child's response to parent behavior.

Methods Employed: Scales have been constructed that give information on twenty-six components of both maternal and paternal behavior. The scales have been administered to 85 normal boys, 80 normal girls, and 81 delinquent boys. Internal consistency reliabilities and scale intercorrelations have been computed for all groups.

Major Findings: Analyses of internal consistency reliabilities for the scales reveals good measurement of individual differences in perception of parents. Reliabilities of the ten item scales range from .46 to .93 with a median of approximately .76. Intercorrelations of the scales reveal that two major dimensions of the child's

Part A

Major Findings (Continued): perception of parent behavior are being measured--love versus hostility and autonomy versus control. The love dimension is best represented by Positive Evaluation of the Child, Expression of Affection, Equalitarian Relationship, and Sharing. Hostility is best represented by Negative Evaluation of the Child, Rejection, Neglect, and Ignoring. Autonomy is best represented by Lax Discipline and Extreme Autonomy; and Control by Strictness, Punishment, Intrusiveness, Direction, and Suppression of Aggression. Other scales also appear to be measuring components of these two bipolar dimensions. These findings therefore replicate the conceptual structure found in an earlier project from ratings of maternal behavior from observations and interview. An unanticipated finding of this research is that children tend to describe parents as similar in their behavior toward them, i.e., if mother is described as hostile or controlling, there is a strong tendency to describe the father as also hostile or controlling. Significant differences between the delinquent and normal boys have also been found but since the groups are not matched for social class or other variables, this difference must be investigated further. However, in the normal groups the education of parents was not significantly related to their children's description of their behavior.

Scientific Significance to the Program of Mental Health Research: This inventory provides another method for investigating hypotheses about parent-child relationships. If validity can be demonstrated in further studies, the inventory might be useful in screening, and in clinical practice for investigating the antecedents of maladjustment. For the present, the inventory will be limited to research use.

Proposed Course of Project: A description of the development of the inventory will be published to make the instrument available to other investigators. The inventory will be used in future research by the investigator in order to determine the relationship of the scales to other aspects of child behavior and to other data on parent-child relationships.

Part B included No

Serial No. M-P-D(C)-27
1. Laboratory of Psychology
2. Section on Child Development
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Predictions of Growth and of Adult Height.

Principal Investigator: Nancy Bayley

Other Investigators: None

Cooperating Units: None

Man Years (calendar year 1960):
Total: .00
Professional: .00
Other: .00

Patient Days:
None

Project Description:

Objectives: This study was undertaken to carry out an assignment for participation in a three-day seminar on the Growth of the Normal Child in the First Three Years of Life, held in Zurich, October 5-7, 1960, under the auspices of the International Children's Center, of Paris. The child's height is one of the many useful criteria for determining normal status or in diagnosis of pathological deviations. The question to be explored here is at how early an age can we predict the course of later growth, and thus detect significant deviations from the normal.

Methods Employed: The heights and skeletal ages (read from X-rays), at annual intervals from birth to 18 years or maturity, from two normal longitudinal samples were analyzed. The data for one sample, of 67 boys and 67 girls was made available by Dr. Harold Stuart of the Harvard University School of Public Health, who has conducted a longitudinal study on a group of children in Boston. The other sample, of 26 girls and 25 boys had been measured by the principal investigator in Berkeley, California between 1928 and 1954.

The percentage of his own adult height for each earlier measuring was computed for each child. Means and S.D.'s of these percentages were then computed for each chronological age and for each skeletal age for the total group. Selections were made of groups of children who were consistently accelerated or retarded in skeletal age, and these groups were compared, with particular reference to the first

Part A

Methods Employed (Continued): four or five years. On the basis of the mean per cent of mature height for a given age, predictions of adult height were computed for each child from his own height at each year one through four years, and the error of prediction was computed. On the Berkeley Growth Study cases, for whom parents' heights were available, the predictions were corrected by a regression formula that takes into account the parents' heights (as there is a correlation of about .5 between heights of parents and their children).

Major Findings: In the first four years skeletal maturity appears to be related to per cent of adult height in girls but not in boys. Prediction from C.A. alone averages about 2% and is most accurate at three years. When parents' heights are taken into account this error is reduced for years 1, 2 and 3, to an average of 1.6% for girls and 1.9% for boys. There remain a few children whose growth rates are irregular and for whom the error of prediction may be as great as 6 or 7%. Reasons for this were considered, primarily the relative influence of different hormonal functions at three successive age periods that are indicated by points at which changes in rates of growth are most likely to occur. The genetic and thyroid hormones tend to predominate in the first three or four years, the pituitary growth hormone from four to nine or 10 years and the gonadal hormones in puberty.

Scientific Significance to the Program of Mental Health Research: In addition to pertinence of these studies for physical diagnosis, there are often strong emotional components in the adjustment of exceptionally tall or short children to their condition of being deviants. The emotional components may occur in the parents' concern about their children as well as the children's concern about themselves. With early prediction, sometimes corrective measures can be taken, or else education for emotional adjustment and acceptance of state can be instituted.

Proposed Course of Project: The report given at the seminar is to be published in the proceedings. A more thorough analysis will be made of the data, including the relations of weight to variations in height and skeletal ages in the preschool years and to prediction of later status.

Part B included Yes

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B

Publications other than abstracts from this project:

Bayley, Nancy: The accurate prediction of growth and adult height. In: Proceedings of the Seminar on Children's Growth in the First Three Years. (Accepted for publication)

Publications Not Directly Related to This Project:

Bayley, Nancy: The development of abstract thinking, learning ability, and reasoning--problems in evaluating these abilities. In: Proceedings of the Maryland Child Growth and Development Institute, Baltimore, Maryland, June 1-5, 1959, pp. 63-68.

Bayley, Nancy: Current research relating to children at the National Institutes of Health. Child Develpm. 31: 209-214, 1960.

Bayley, Nancy: Mental development. In Harris, C. W. (ed.): Encyclopedia of Educational Research (ed. 3). New York, Macmillan, 1960, pp. 817-823.

Serial No. M-P-P-(C)-6
1. Laboratory of Psychology
2. Section on Personality
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Development of an Ego-integration Conceptual System for Studying Psychotherapy

Principal Investigator: Donald S. Boomer, Ph.D.

Other Investigators: D. Wells Goodrich, M.D. and Joseph Handlon, Ph.D.

Cooperating Units: Biosocial Growth Studies Branch
Community Psychiatric Clinic
Department of Psychology
University of Michigan

Man Years (calendar year 1960):		Patient Days (calendar year 1960):
Total:	2.51	540 Outpatients
Professional:	1.00	
Other:	1.51	

Project Description:

Objectives: 1. To develop a conceptual model for studying one aspect of the therapeutic process, namely the development of the relationship between patient and therapist. Of especial interest are changes, both long-term and moment-to-moment, in the patient's freedom to communicate about his direct interpersonal experience with the therapist. 2. To develop some concrete measures of manifest behavior which relate to the patient's ability to experience and to communicate about his relationship with the therapist. Thus far these efforts have been focused on non-lexical, or expressive aspects of the patient's speech. 3. To bring together (1) and (2) in the sense that the operations and measures developed under objective (2) can be utilized to test the adequacy of the conceptual model described under objective (1).

Methods Employed: Electrical tape recordings of psychotherapy interviews and transcriptions of these interviews provide the basic data concerning non-lexical aspects of patient speech.

The primary focus of the study to date has been the incidence of influencies or disturbances in the word-to-word flow of speech. These are scored by listening to the tape recordings and marking the

Part A

Methods Employed (Continued): disturbances on a written transcript.

Additional methods, now in the exploratory phase, include (1) electrical recording of the patient's breathing during interviews, and (2) the use of computer data-processing of word-use frequencies in order to measure stereotypy of speech. The place of these new methods in the overall project will be explicated in the section of this report entitled Proposed Course of the Project.

Patient Material: Six outpatients are being seen currently in connection with this project:

A. Female	Dr. Goodrich	Four times a week
B. Female	Dr. Goodrich	Two times a week
C. Male	Dr. Goodrich	One time a week
D. Female	Dr. Boomer	Three times a week
E. Female	Dr. Boomer	Two times a week
F. Male	Dr. Handlon	Two times a week

Major Findings: A study, replicating Mahl's (J. abn. Soc. Psychol. 1956) original work on the speech disturbance measure has been completed and written up. The report of this study is now in press. (J. Consult. Psychol., April 1961)

The results of this study were tentatively included in last year's Annual Report and will not be repeated here. In general they provided only equivocal support for Mahl's thesis that the speech disturbance ratio is a direct measure of anxiety. The replication study also indicated the pressing need for more reliable and objective criterion measures in order to explore the psychological meaning of speech disturbance. The development of improved criteria is the present aim of this project.

No major findings have emerged from this project during the past year. Several criteria for anxiety have been tried and discarded. The hope that delayed auditory feedback would produce speech disturbances similar enough to warrant their study proved unfounded. Progress has thus been conceptual and methodological, rather than substantive.

Scientific Significance to the Program of Mental Health Research:

The systematic investigation of psychotherapy is a salient part of the program of NIMH. The Ego state project may contribute to this effort directly with substantive findings or indirectly with methodological and conceptual developments which can be utilized in other parallel investigations.

Part A

Proposed Course of the Project: Three main lines of investigation will be pursued in the coming year:

1. A set of experimental interviews conducted by Dr. Jesse Gordon, University of Michigan, are being studied for speech disturbances. These interviews were done following hypnotic induction of the subjects. With regard to a specific conflict each subject had on three different occasions the post-hypnotic suggestion to (1) forget, (2) remember but suppress and, (3) remember and discuss the conflict.

When these data are analyzed they will be compared with continuous skin conductance data which Dr. Gordon is analyzing.

2. Exploratory work is being carried out with one patient on a speech-breathing measure developed by Golman-Eisler. The data for this measure are fluctuations in the number of words spoken per inspiration, with the general assumption that anxiety will decrease the efficiency of breath utilization and, thus, decrease the words/ inspiration ratio.

If this proves to be a useful measure, it will be compared with speech disturbance data.

3. Stereotypy of language usage as a defensive maneuver will be studied in the third type of investigation. Work is now under way to establish computer data programming which will yield a continuous quantitative measure of stereotypy-flexibility in the patient's choice of language.

If successful, this measure will reflect another meaningful non-lexical aspect of patient speech, and its parameters will be explored in the context of the total research program.

Part B included Yes

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B Honors, Awards, and Publications

Publications other than abstracts from this project:

Boomer, D. S., and Goodrich, D. W.: Speech disturbance and judged anxiety. J. Consult. Psychol. 1961 (In press)

Serial No. M-P-P-(C)-7
1. Laboratory of Psychology
2. Section on Personality
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Patterns of Responses on Psychodiagnostic Tests Yielded by Patients Suffering From Various Psychosomatic Diseases

Principal Investigator: Joseph H. Handlon, Ph.D.

Other Investigators: None

Cooperating Units: None

Man Years (calendar year 1960):
Total: 1.46
Professional: .50
Other: .96

Patient Days (calendar year 1960):
None

Project Description:

Objectives:

General: To study the relationships between individual personality structure and susceptibility to the various psychosomatic diseases.

Specific: As a preliminary to further study of this problem, a complete survey of the results of previous studies relating patterns of responses on psychodiagnostic tests to specific psychosomatic diseases is to be made.

Methods Employed: During the past year the project has continued with the survey of pertinent literature in which specific responses to psychological tests by individuals suffering from typical psychosomatic diseases have been reported. Since there are an increasing number of such studies being published, a major portion of time is devoted to the making of a precis of each study. During the past year a coding system has been worked out along with a mechanical method of storing the data which will now permit the ready manipulation of the large mass of data gleaned.

Part A

Major Findings: Coding system was found inadequate for the aims of the study.

Scientific Significance to the Program of Mental Health Research: It is hoped that the results of this study will shed some light on the etiology, general dynamics of, and the appropriate therapeutic interventions necessary for psychosomatic illness. It is also hoped that more refined diagnostic methods may be discovered which will make for more accuracy in the early discovery of the disease, as well as the specifying of personality types who would be likely to fall victim of such illnesses with an eye to preventing such an occurrence.

Proposed Course of Project: This project has been indefinitely suspended pending the development of a more satisfactory coding system. The urgency of other work which appears more fruitful makes it unlikely that work on this project will be resumed soon.

Part B included No

Serial No. M-P-P-(C)-9
1. Laboratory of Psychology
2. Section on Personality
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: An Analysis of Interpersonal Communication Patterns Within Families of Schizophrenics and Non-Schizophrenics in Group Situations

Principal Investigator: Joseph H. Handlon, Ph.D.

Other Investigators: Morris B. Parloff, Ph.D.
Lyman C. Wynne, M.D., Ph.D.

Cooperating Units: Adult Psychiatry Branch

Man Years (calendar year 1960):
Total: .46
Professional: .35
Other: .11

Patient Days (calendar year 1960):
None

Project Description:

Objectives: There is evidence to suggest that there may be interpersonal communication patterns which are unique to families one of whose members is a schizophrenic. It will be the purpose of this study to attempt to demonstrate these assumed differences both in group therapy situations where the group is made up of family members, and in more structured quasi-experimental group situations. Attempts will then be made to relate these differences to the etiology of schizophrenia.

Methods Employed: During the past year the focus of the project has been primarily upon attempts at explicating some of the theoretical and methodological problems in studying the communication patterns of families of schizophrenic patients in a group therapy setting. Experience with family group therapy was drawn upon and generalizations from clinical experience were objectively supported through taped recordings of the sessions themselves.

Major Findings: Many special problems stemming from the use of family psychotherapy group sessions both as a therapeutic method and as a research tool have been specified. In contrast to the usual psychotherapy and experimental group, the family constellation has an ongoing history, a high degree of interpersonal involvement, shared

Part A

Major Findings (Continued): interpersonal distortions, and a unique communication system. The implications for the researcher who often has the role, also, of the therapist has been drawn.

Scientific Significance to the Program of Mental Health Research:

If it is the case that the intra-family dynamics play a crucial role in the course of schizophrenia, then a careful study of these dynamics under controlled conditions would seem to be profitable. It will be particularly important to determine whether such consistent intra-family communication patterns as are found are really unique to families of schizophrenics, or whether they are to be found in non-schizophrenic families as well. If found in both schizophrenic and non-schizophrenic, is there a difference in degree? A correlative question is that of whether such patterns as may be found are a result of having a mentally disturbed member in the family, or whether they are an important contributing factor in the actual development of schizophrenia.

Proposed Course of the Project: Project terminated.

Part B included Yes

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B Honors, Awards, and Publications

Publications other than abstracts from this project:

Handlon, J. H.: A meta-theoretical view of assumptions regarding the etiology of schizophrenia: implications for research. A.M.A. Arch. Gen. Psychiat. 2: 43-60, 1960.

Handlon, J. H., and Parloff, M. B.: The treatment of patient and family as a group: is it group therapy?. Int. J. group Psychother. 1960. (In press)

Parloff, M. B.: The family in psychotherapy. A.M.A. Arch. Gen. Psychiat. (Accepted for publication)

Serial No. M-P-P-(C)-13
1. Laboratory of Psychology
2. Section on Personality
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1959

Part A

Project Title: Utilization of Creative Potential

Principal Investigator: Morris B. Parloff, Ph.D.

Other Investigators: Albert J. Caron, Ph.D.
Sanford Unger, Ph.D.
Dr. Jacob Fishman
Dr. Fred Snyder

Cooperating Units: Clinical Investigations

Man Years (calendar year 1960):
Total: 1.81
Professional: 1.10
Other: .71

Patient Days (calendar year 1960):
25

Project Description:

Objectives: To investigate the psychological processes, internal and external, which are necessary and sufficient for creative thought.

Methods Employed: The research combines two approaches: 1. intensive clinical investigations of individuals who have been designated as creative or potentially creative and 2. to study those psychological processes relevant to creative thinking.

Specific:

1. Intensive psychoanalytic investigation of a gifted and potentially "creative" individual.

2. Adaptation of Kleitman's technique of monitoring the dreams of individuals who have failed to solve problems administered immediately prior to their retiring.

3. Utilization of hypnotic suggestion to alter states of motivation and self-confidence.

Part A

Major Findings:

1. Psychoanalytic investigation of this patient reveals powerful inhibition of and control over any novel creative self expression as this is behavior which could overthrow the parental standards and might therefore result in destroying the parent and other authority figures.

2. The dream monitoring techniques have not revealed any evidence of the subject "working" on problems in the dream state. The obscuring factor of symbolic representation may make this avenue of study more difficult as it provides quite ambiguous data.

3. There is some evidence that the patient under the influence of hypnotic suggestion of increased self-confidence may improve his cognitive performance in fluency and novelty of relevant associations to problems. Additional controls are now being introduced to assess the relative enhancement of a variety of self-instructions which may be implicit in the general suggestion of "self-confidence".

Scientific Significance to the Program of Mental Health Research:

The problem of enhancing the creativity of the research scientist is of vital importance to the nation and the agencies which undertake the conduct of research. In the proposal outlined above it is assumed that one way of increasing the research potential of the nation is not only to identify and encourage the most creative individuals but to investigate the possibility of devising techniques to make even lesser creative individuals free enough to use their potential.

Proposed Course of the Project: The above investigation will be pursued with particular emphasis on understanding the psychological processes involved.

Part B included Yes

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B Honors, Awards, and Publications

Publications Not Directly Related to This Project:

Parloff, M. B.: The impact of ward-milieu philosophies on nursing-role concepts. Psychiatry. 23: 141-151, 1960. (This publication is related to a project which was completed in 1957: Serial No. M-P-P-(C)-2).

Serial No. M-P-P-(C)-14
1. Laboratory of Psychology
2. Section on Personality
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Motivational Factors in Learning and Thinking

Principal Investigator: Albert J. Caron, Ph.D.

Other Investigators: None

Cooperating Units: Montgomery County School System

Man Years (calendar year 1960):		Patient Days (calendar year 1960):
Total:	1.01	None
Professional:	.65	
Other:	.36	

Project Description:

Objectives:

1. General: To assess the relationship between motivational aspects of personality structure and such cognitive variables as knowledge-seeking behavior, comprehension of complex principles and problem solving.

2. Specific: To compare the effectiveness of intrinsic motivation (desire to learn for its own sake) and extrinsic motivation (desire to learn for an ultimate payoff in external standards of evaluation, e.g. grades, success, recognition, etc.) on the learning and comprehension of complex scientific principles.

Methods Employed: The subjects were some 1200 tenth grade students in the Montgomery County School system, tested in three separate 50 minute class sessions during the spring of 1960. The major independent variables were (1) IQ level, (2) sex, and (3) Intrinsic versus Extrinsic motivation. The latter variable was indexed in two ways: (a) by experimental manipulation of the conditions of learning and (b) by inference from scores on various tests of motivation designed to assess the intensity of the individual's investment in external criteria of performance. The major dependent variables were (1) a "comprehension" score and (2) a "rote memory" score, both derived from a test on abstract material previously studied for 15 minutes. The

Part A

Methods Employed (Continued): comprehension questions were designed to assess the subjects' functional understanding of a complex principle by having them apply it to new problems. The rote questions were designed to assess their memory for facts and definitions. The learning material was a simplified version of an actual psychological theory - Atkinson's Theory of Risk Taking.

The motivation tests included (1) the TAT measure of need Achievement, (2) the Mandler-Sarason Test Anxiety scale, (3) Atkinson's recently devised Risk Taking Questionnaire, and (4) a "Student -Attitude Questionnaire" developed by the principal investigator to measure the relative importance to the individual of such Ego-ideal areas as Intelligence, Creativity, Wealth, Influence, Physical Appearance, etc. Supplementary data, in this same genre, included ratings by teachers of the individual's "Desire for Grades" and "Desire for Understanding" as well as a measure of academic over-and under-achievement indexed by the sigma score differential between IQ and actual grades (obtained from the school records).

The experimental manipulation of extrinsic and intrinsic motivation was conducted by means of instructions which aroused a test-taking orientation in half the sample (the Extrinsic group) and a curiosity or interest orientation in the other half (the Intrinsic group).

Major Findings: Complete analysis of the data must await a factorial treatment of the motivational variables so that the optimal selection of conative measures for indexing intrinsic and extrinsic propensities may be made. This phase of the analysis is now being prepared for processing by computer techniques. However, a provisional analysis has been undertaken for the independent variables of Extrinsic-Intrinsic condition, IQ, Test Anxiety, and Sex. This analysis has been partially completed with the following findings:

(1) INTRINSIC-EXTRINSIC COMPARISON: In accordance with hypothesis, Extrinsic subjects overall were superior to Intrinsic subjects in rote performance. Contrary to hypothesis, however, Extrinsic subjects also tended to be superior in comprehension, although not to as great a degree.

Among high IQ subjects (119 and above), subdivided into three levels of test anxiety (high, middle, and low), only for the high test anxiety subgroup was the Extrinsic condition reliably superior to the Intrinsic condition in comprehension. Among middle IQ subjects (108-118), the reverse was the case; only for the low test anxiety subgroup was the Extrinsic condition reliably superior. With respect

Part A

Major Findings (Continued): to rote performance, for both high and middle test anxiety subjects at both IQ levels, the Extrinsic condition was reliably superior.

Thus, a striking difference between rote and comprehension performance was found for the middle IQ groups where high and middle test anxiety subjects showed little difference in comprehension between Extrinsic and Intrinsic conditions but a vast difference in rote memory in favor of the Extrinsic condition and, conversely, where low test anxiety subjects showed little difference in rote performance but a significant difference in comprehension in favor of the Extrinsic condition. Apparently anxious subjects with marginal IQ's, when learning material under ordinary test-grade incentives, resort to memorization at the expense of understanding. Non-anxious subjects with marginal IQ's under these same incentives place greater emphasis on comprehension.

The failure to find any overall superiority of the Intrinsic condition in comprehension may have been due to the fact that intrinsic arousal was not as generally intense as extrinsic arousal and thereby produced a differential in exposure in favor of the Extrinsic subjects.

(2) TEST ANXIETY AND SEX COMPARISONS: Boys low in Test Anxiety do significantly better in comprehension than boys high in Test Anxiety in both Intrinsic and Extrinsic conditions, but there is no difference for the comparable groups of girls. Girls in the middle range of Test Anxiety tend to outperform both high and low anxious girls, but middle anxious boys are intermediate between low and high anxious boys. The same relationships hold for rote performance with the exception that there are no significant differences between any of the male anxiety groups in the Extrinsic condition. Why test anxiety should affect performance differentially for the males and females, particularly in the low anxiety range, is unclear at present. It could be that low test anxiety girls are spurious lows (given that their performance is similar to high anxiety girls) or that they are in general intellectually unmotivated.

(3) FURTHER SEX COMPARISONS: In the Intrinsic condition, low test anxiety males are significantly superior to low test anxiety females in comprehension and high and middle anxiety males are about equal to the comparable female groups. With respect to rote scores, however, females (particularly in the middle IQ range) significantly outperform males. A similar pattern prevails in the extrinsic condition. Superior academic performance of females at all educational levels has been a consistent finding in the literature. The present data suggest that this superiority is confined to rote memory performance and not to functional understanding of abstract principles.

Part A

Scientific Significance to the Program of Mental Health Research:

Mental Health research has concerned itself historically with the factors affecting deviation from normalcy in an abnormal direction, i.e. with the factors contributing to mental illness. In this context mental health tended to be defined negatively as the absence of mental illness. To the extent that optimal mental functioning -- not merely non-deranged or "normal" functioning -- is also part of the province of mental health research, the present study -- concerned as it is with the factors facilitating creative cognitive performance-- is manifestly pertinent to the overall program.

Proposed Course of Project: The project will move in two major directions. First, a factor analysis of all motivational measures will be undertaken in order, by assessment of the dimensionality of these measures, to obtain an optimal index of extrinsic propensity. Secondly, a number of additional experiments are planned with the following aims: (1) to attempt to heighten the intensity of curiosity arousal in the intrinsic condition so that exposure to the learning material will be more equal to that occurring in the extrinsic condition; (2) to determine the motivational differences between low test anxiety boys and girls; (3) to test the hypothesis that girls are more rote oriented than boys; (4) to determine whether the poor performance of high test anxiety boys in the intrinsic condition is a function of inferior learning or of anxiety at the time of testing; (5) to study more generally the factors affecting the arousal of curiosity and subsequent knowledge-seeking.

Part B included No

Serial No. M-P-P-(C)-15
1. Laboratory of Psychology
2. Section on Personality
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year

Part A

Project Title: Effects on Creative Problem Solving by Dyads of Degree of Mutual Respect and Nature of Interaction

Principal Investigators: Morris B. Parloff, Ph.D. and Joseph H. Handlon, Ph.D.

Other Investigators: None

Cooperating Units: Clinical Investigations
Laboratory of Clinical Services

Man Years (calendar year 1960):		Patient Days (calendar year 1960):
Total:	1.61	24
Professional:	.75	
Other:	.86	

Project Description:

Objectives: To investigate the interactive effect of degree of mutual respect and degree of criticalness upon the production of members of dyadic teams attempting to solve open-ended problems.

Methods Employed: Subjects (young women of college age) who have lived together in a dormitory-like situation for a period of two months are formed into two member teams in terms of the degree of mutual respect as measured by sociometric methods. As a team they are required to solve a series of open-ended problems (those for which there is no single "correct" solution). Each dyad is instructed to solve some problems under the conditions where they are critical of each other's work, and other problems where they are supportive and uncritical. Examples of critical and uncritical interactions are demonstrated to the dyads by means of tape-recorded examples. A day or two prior and again immediately prior to the running of the team experiment, each of the subjects has attempted to solve the problem individually. This is done in order to get some estimate of the individual ability and to force the seeking of new solutions in the team situation. Both the individual and the team solutions to the problems are rated by judges as to the quality of the answers in order to determine whether the hypothesized factors have effect upon the productions.

Part A

Major Findings: A pilot study was run during the summer of 1959 which yielded suggestive enough results so that the study was replicated with a comparable group in the summer of 1960 in order to complete a balanced experimental design. While the analysis of the material from the first group has been almost completed, the analysis of the material from the combined groups is now being worked upon. Results thus far suggest that the quality of the performance of subjects is affected by the nature of the instructions as to the amount of criticalness to be shown towards the partner. The less critical the interaction the greater the output of the team in terms of both high and low quality solutions. However, the instructions regarding the criticalness seems to have more effect upon the performance of the low mutual respect groups than it does upon the high mutual respect groups.

Scientific Significance to the Program of Mental Health Research:

Because of the ever-increasing amount of specialization in all fields of scientific endeavor (including that of NIH),it is becoming more and more necessary to rely upon the team approach toward the solution of research problems. The history of such research teams shows that they vary a great deal as to the degree of productivity, but the factors which go into the making of successful teams is as yet a good deal of a mystery. The current project is an attempt to uncover such factors in a rigorous manner by making use of a simplified yet meaningful problem solving situation where the several factors hypothesized as being critical can be experimentally manipulated.

Proposed Course of the Project: The analysis of data will be continued and a report of the findings prepared. It is assumed that any definitive findings will suggest other hypotheses to be pursued. As more factors reveal themselves in experimental situations as being critical for team productivity, it is hoped that the studies can be broadened to include presently functioning actual research teams in a variety of scientific areas.

Part B included No

Serial No. M-P-P-(C)-16
1. Laboratory of Psychology
2. Section on Personality
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Uncertainty, Epistemic Curiosity and Retention

Principal Investigator: Daniel E. Berlyne, Ph.D.

Other Investigators: None

Cooperating Units: Montgomery County School System

Man Years (calendar year 1960):		Patient Days (calendar year 1960):
Total:	.84	None
Professional:	.33	
Other:	.51	

Project Description:

Objective: To obtain information about the workings of epistemic curiosity as a preliminary to studying the role of curiosity in creative thinking.

Methods Employed:

General: The project was guided by a theory according to which epistemic (or intellectual) curiosity increases with degree of conflict between symbolic response-tendencies. The information-theoretic variable, uncertainty (entropy), was used as a principal independent variable because this variable reflects two of the quantities on which degree of conflict is assumed to depend, viz. number of competing alternatives and approximation to equality of strength of competing alternatives. Verbal reports of strength of desire to know the answers to questions and retention of answers after they have been supplied were the two principal dependent variables, since previous experiments showed these to be useful manifestations of the strength of curiosity.

Experiment I: A list of 30 quotations was prepared. Each quotation was associated with the names of two or three figures from history or literature, represented as possible authors. Subjects were told that the quotations had been shown to a group of 100 high school teachers, and after each potential author's name there was a number

Part A

Methods Employed (Continued): purporting to be the number of teachers out of 100 who selected it as the name of the true author. The alleged distributions of teachers' guesses approximated 90/10, 50/50, 77/13/10, and 33/33/33 for 10, 5, 5 and 10 quotations respectively. These distributions correspond to 0.5, 1, 1, and 1.6 bits of uncertainty respectively.

Subjects were asked to select and rank-order the 12 quotations out of 30 whose true authors they would most like to know. Half of them were also asked to indicate a guess respecting the true author before completing this task.

Experiment II: Subjects were exposed to the same material as was used in Experiment I. They then heard the quotations read once again, each coupled with the name of the allegedly true author. Finally they were tested for retention of the "true" authors and given an "extended-curiosity" test, in which the names of the 30 "true authors" were listed, and subjects had to indicate which of them they would like to know more about.

The quotations were presented orally and the alleged possible authors and distributions of teachers' guesses were read by subjects while listening to the quotations. One group of subjects was told to indicate a guess with respect to the true author as soon as each quotation had been heard, while another group was not told to do so. One sub-group of each of these groups had the "immediate" conditions, i.e. the alleged true author was supplied immediately after each quotation was first presented and before going on to the next quotation, while another sub-group had the "delayed" condition, i.e. all the quotations were first presented, and then all the "true" authors were supplied.

Major Findings:

Experiment I:

1. Degree of curiosity expressed was found to increase with uncertainty. Further analysis showed, however, that curiosity was greater when there were three alternative authors than when there were two, but there was no significant effect of evenness of distribution.

2. The distributions of guesses for the quotations in the various uncertainty categories were examined. It emerged that a. The distributions were affected by the alleged distributions of teachers' guesses. b. There was a tendency to select the author named first more frequently than others. c. With uneven distributions, the distribution of subjects' guesses was more even than the distribution

Part A

Major Findings (Continued): of alleged teachers' guesses. This latter phenomenon may well explain why evenness of distribution had no significant effect on degree of curiosity expressed: the differences in response uncertainty (which is the most meaningful measure of the degree of conflict actually induced) were considerable between three-alternative and two-alternative questions, but very small between questions with even and uneven distributions of alleged teachers' guesses.

3. The relation between the independent variables and curiosity was not influenced by the presence or absence of instructions to guess.

Experiment II:

1. Analysis of retention scores showed retention to be significantly greater with the guess condition than with the no-guess condition and with the delayed than with the immediate. Retention was not affected by the uncertainty associated with a quotation.

2. Extended curiosity was greater with the guess condition than with the no-guess condition. When the covariance between extended curiosity and retention score was taken into account, the extended-curiosity scores were higher than expected for the immediate condition and lower for the delayed condition.

3. There was a significant positive correlation between IQ and retention, a significant positive correlation between extended curiosity and retention, and no significant correlation between extended curiosity and IQ.

4. The data are consistent with the view that there is a motivational ("curiosity" or "attention") factor which is independent of IQ and which is reflected in both retention scores and extended-curiosity scores. It is affected by the conditions in which questions are presented to subjects. But further experimentation is required to confirm this view.

Proposed Course of Project: Project terminated as the investigator's appointment as visiting scientist expired September 1960.

Part B included No

Serial No. M-P-P-(C)-17
1. Laboratory of Psychology
2. Section on Personality
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Collative Variables and Arousal

Principal Investigator: Daniel E. Berlyne, Ph.D.

Other Investigators: None

Cooperating Units: None

Man Years (calendar year 1960):		Patient Days (calendar year 1960):
Total:	.77	10
Professional:	.33	
Other:	.44	

Project Description:

Objectives: 1. To investigate the relations between collative properties of stimuli and the magnitude of the orientation reaction (a transient rise in the level of arousal). The collative variables include novelty, surprisingness, complexity and power to induce uncertainty. 2. To test the hypothesis that the influence of collative variables on arousal depends on the fact that high values of all the collative variables can be assumed to involve conflict. It is necessary, in order to test this hypothesis, that a form of conflict be used which is arbitrary and isolates degree of conflict from other variables that might affect arousal.

Methods Employed: The galvanic skin response and finger volume were used as components of the orientation reaction or indices of the level of arousal. Of these the latter did not yield reliable data, so that the following discussion will be confined to the former.

Experiment I: The apparatus, apart from equipment for recording the psychophysiological data, consisted of a vertical board bearing eight lights, two at each corner of a diamond, and a key that could be pressed in any of four directions, corresponding to the four corners of the diamond.

The experiment compared forced-choice reactions, in which the lights at one corner light up and the subject has to press the key in the corresponding direction, with free-choice reactions, in which

Part A

Methods Employed (Continued): lights appear at two corners and the subject has to respond to either of them, the choice being left to him. The free-choice situation is regarded as a high-conflict situation, but degree of conflict was isolated from differences in novelty, surprisingness, and intensity. There was also a preliminary phase when the stimulus patterns were presented, but no response was required. This was to separate effects of degree of conflict from effects of differences between the forced-choice and free-choice stimulus patterns as such, e.g. differences in complexity.

The stimulus patterns were on for 10 seconds with 11 second intervals between them, and subjects were instructed to respond as soon as the lights went off.

Experiment II: A word-association test was used, the words being selected from Laffal's (1955) study of effects of response uncertainty (entropy). Laffal examined the distributions of responses given to each word by a large group of subjects, calculating from each distribution a measure of response uncertainty. The present experiment compared effects of high-uncertainty and low-uncertainty words, response uncertainty being regarded as a measure of degree of conflict.

Experiment III: The same apparatus as in Experiment I was used. Subjects received a series of visual stimuli, consisting of lights appearing at two corners of the diamond in turn. But at one point, a light appeared at one corner when a light at the other corner was expected in accordance with the alternation that had occurred hitherto. This light was thus surprising but it was not novel, since a similar stimulus had just appeared in an expected temporal location. Subjects had one phase in which they had to respond to the stimulus patterns with corresponding key-pressing responses and one phase in which no response was required.

Experiment IV: The material consisted of visual figures, previously used in an experiment on exploratory behavior. The figures differed according to variables that might be regarded as forms of complexity. More and less complex figures were presented in random order, and subjects had merely to look at them. Each figure appeared for 20 seconds with 20-second intervals.

Major Findings: 1. In Experiment I, high-conflict trials produced significantly greater galvanic skin responses (GSRs) than low-conflict trials. This difference did not appear during the preliminary phase without overt responses, and so it can be taken to represent an effect of degree of conflict. 2. In Experiment II, high-uncertainty words produced greater GSRs than low-uncertainty words. 3. These last

Part A

Major Findings (Continued): two findings confirm that degree of conflict affects the magnitude of the orientation reaction and are thus compatible with the hypothesis that the effects of other collative variables are due to conflict. 4. In Experiment III, stimulus patterns that were surprising without being novel produced greater GSRs than others, confirming that surprisingness as such influences the level of arousal. The effect appeared with equal prominence whether or not the stimuli were signals for overt responses, suggesting that surprising stimuli are arousing even when they have no special implications for overt behavior. 5. In Experiments I and III, GSRs were greater when an overt response was required than when no overt response was required. 6. In Experiment IV, no significant differences appeared between GSRs to more and less complex figures. But it seems that an effect might emerge if the figures were given very brief exposures and shown repeatedly. It is hoped to perform this experiment during the coming academic year at Boston University.

Proposed Course of Project: Project terminated.

Part B included Yes

Serial No. M-P-P-(C)-18
1. Laboratory of Psychology
2. Section on Personality
3. Bethesda

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A

Project Title: Conflict and Reaction Time

Principal Investigator: Daniel E. Berlyne, Ph.D.

Other Investigators: None

Cooperating Units: None

Man Years (calendar year 1960):
Total: .68
Professional: .24
Other: .44

Patient Days (calendar year 1960):
12

Project Description:

Objectives: To study the effects of stimulus intensity on reaction time and the effects of number of competing alternative responses on reaction time.

Methods Employed: The apparatus consisted of a vertical board bearing eight lights, two at each corner of a diamond, and key that could be pressed in any of four directions corresponding to the corners of the diamond.

In two experiments, free-choice reactions were intermingled with forced-choice reactions. In Experiment I, three levels of intensity were used for free-choices and two for forced-choices. In Experiment II, there were free choices involving 2, 3, and 4 alternatives.

Major Findings: 1. Free-choice reaction-times were longer than forced-choice reaction-times, and forced-choice reaction-times were longer with dimmer stimuli, both of which findings confirm what was found in the previous experiments. 2. Neither intensity of stimuli nor number of alternative response was found to affect free-choice reaction-time.

Proposed Course of Project: Project terminated.

Part B included No

Serial No. M-CS-OC(C)-1
1. Laboratory of Clinical Science
2. Office of the Chief
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: A program on the biological aspects of schizophrenia and other mental disorders.

Principal Investigator: Seymour S. Kety

Other Investigators: See individual projects.

Cooperating Units: See individual projects in the Laboratory of Clinical Science, NIMH, as follows: Section on Psychiatry, M-CS-Ps(C)-4,5,6 and 8; Section on Physiology, M-CS-P(C)-8; Office of the Chief, M-CS-OC(C)-2,3,4 and 7; Section on Medicine, M-CS-M(C)-5 and 7.

Man Years (calendar year 1960)		Patient Days (calendar year 1960)
Total:	2.0	See individual projects
Professional:	1.0	
Other:	1.0	

Project Description:

Objectives: To stimulate, coordinate and direct a multidisciplinary program of biochemical, pharmacological and physiological studies in schizophrenia and other mental disorders and their correlation with psychological and psychiatric aspects of the disease. The program involves the evaluation of reported biological abnormalities, but, more important, the development and testing of new hypotheses concerning the operation of biological factors in this disease.

Methods Employed: See individual reports of the various sections.

Major Findings: See individual reports of the various sections.

Project Description (continued):

Significance to Biomedical Research and the Program of the Institute: The findings of recent studies assign an important role to genetic factors in the schizophrenic psychoses. Increased knowledge of intermediary metabolism, the development of chromatographic, isotopic and electrophysiologic techniques makes worthwhile a critical examination of biological factors in schizophrenia and other mental disorders, as well as in normal personality and behavior.

Proposed Course of Program: The program is one of long duration. During the coming year attention will continue to be devoted to particular aspects of intermediary metabolism where deviations from the norm have been found or confirmed by studies in the Laboratory on schizophrenic patients, or which, on the basis of present information, appear to be relevant to normal or abnormal behavior. Such studies include a further analysis of the response in schizophrenic patients of blood glucose to epinephrine and of free fatty acids to insulin. It will include further definition of the psychological effects of methionine or tryptophan loading in schizophrenic patients and normal volunteers and an attempt to define the biochemical mechanisms associated with them. The general program of studies on the centrally occurring amines, their metabolism, response to drugs and association with behavioral state will be continued.

Part B included: Yes

Part B: Honors, Awards, and Publications

Publications other than abstracts from this project:

Kety, S.S.: Recent biochemical theories of schizophrenia. The Etiology of Schizophrenia, Jackson, D.D., Ed. Basic Books, New York, 1960 (pp. 120-145).

Kety, S.S.: The possible relationships between the catecholamines and emotional states. The Physiology of Emotions. Charles C. Thomas, Springfield (in press).

Kety, S.S.: An examination of current biochemical concepts of schizophrenia. Chemical Pathology of the Nervous System, Folch-Pi, J., Ed. Pergamon Press, Oxford (in press).

Kety, S.S.: A biologist examines the mind and behavior. The opportunities and limitations confronting the physical sciences in the areas of consciousness and behavior. Science (in press).

Other publications not directly related to this project:

Kety, S.S.: Theory of blood-tissue exchange and its application to measurement of blood flow. Methods in Medical Research VIII, Bruner, H.D., Ed. Year Book Publishers, Chicago, 1960 (pp. 223-227).

Kety, S.S.: Measurement of local blood flow by the exchange of an inert, diffusible substance. Methods in Medical Research VIII, Bruner, H.D., Ed. Year Book Publishers, Chicago, 1960 (pp. 228-236).

Kety, S.S.: The cerebral circulation. Handbook of Physiology American Physiological Society, Washington, D.C., (in press).

Kety, S.S.: The history of concepts regarding the cerebral circulation. Basic Concepts in Cardiovascular Function, Fishman, A.P. and Richards, D.W., Eds. Oxford University Press, New York (in press).

Kety, S.S.: Sleep and the energy metabolism of the brain. Ciba Foundation Symposium The Nature of Sleep. Churchill, London (in press).

Kety, S.S.: Blood flow and metabolism of the human brain in health and disease. Neurochemistry, Elliott, K.A.C., Ed. Charles C. Thomas, Springfield (in press).

Part B (Continued)

Honors and Awards:

Dr. Seymour S. Kety:

Presented 12th NIH Lecture on May 18, 1960, entitled "A Biologist Examines the Mind and Behavior."

Served as Organizing Chairman of the Fourth International Neurochemical Symposium, held in Varenna, Italy, June 13-17, 1960.

Presented Dedicatory Address for the Stanley Cobb Laboratories for Psychiatric Research, Massachusetts General Hospital, Boston, October 14, 1960.

Serial No. M-CS-OC(C)-2
1. Laboratory of Clinical Science
2. Office of the Chief
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A:

Project Title: Comparison of the excretion patterns of aromatic amino acids by normal subjects and by schizophrenic patients.

Principal Investigator: Elwood H. LaBrosse

Other Investigators: Irwin J. Kopin

Cooperating Units: Sections on Physiology, and Psychiatry, and Unit on Psychosomatics

Man Years (calendar year 1960)		Patient Days (calendar year 1960)
Total:	1.10	1488
Professional:	0.40	
Other:	0.70	

Project Description:

Objectives: Urinary metabolites were studies in patients who were on iproniazid and loading doses of amino acids. This study was conceived as a way of testing the hypotheses that amines, especially aromatic amines, have a causative relationship to schizophrenia or play a role in affect, behavior or neutral state.

Methods Employed: The schizophrenic patients were divided into three groups of four members each so that the total body weights of each group were approximately the same. For the second half of the study an additional patient not on Marsilid was added to the study, during this half of the study the dosage of Marsilid was increased to 150 mg/70 kg. of body weight/day. During the seventh month of the study, l-tryptophan and l-phenylalanine were given in increasing doses up to 15 and 20 grams/kg. of body weight/day for 10 days, during the last month of the study dl-5-hydroxytryptophan and dl-3,4-dihydroxyphenylalanine were given intravenously in gradually increasing doses up to 108 mg/day.

Project Description (continued):

The patients were examined for mental symptoms by the Section on Psychiatry and 24 hour urine specimens were collected for study of urinary metabolites.

Patient Material: Twelve male schizophrenic patients were used in this study.

Major Findings: The biochemical study of the urine specimens is still in progress. Findings to date on the urinary excretion of tryptamine and indole acetic acid indicate that the tryptamine/indole acetic acid ratio provides a better index of monoamine oxidase inhibition than does urinary tryptamine alone since the latter is markedly altered by the amount of tryptophan in the diet. Earlier indications that phenylalanine loading produced a significant increase in urinary tryptamine were not confirmed in the second half of the study.

As will be described more fully in a report by the Section on Psychiatry, the administration of methionine produced the most marked psychological reaction in the patients. As an index of methylation the creatine excretion was examined before and during the administration of methionine, but no increase was found. This result indicated either that methylation was not generally increased or that other compounds with potent CNS activity were methylated first.

Studies of the phenolic amines in these urine specimens indicated that there is no readily apparent correlation between phenolic amine excretion and the degree of mental disturbance in the patients.

Significance to Bio-Medical Research and the Mental Health Program: A knowledge of the relationship between urinary amines and mental state of mental patients would provide fundamental information essential for evaluation of the hypothesis that a disturbance in amine metabolism plays a role in the etiology or pathogenesis of schizophrenia.

Proposed Course of Project: Further study on the metabolites of amino acids is in progress and will be examined for their correlation with the degree of mental disturbance in the patients.

Part B included: No

Serial No. M-CS-OC(C)-3
1. Laboratory of Clinical Science
2. Office of the Chief
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A:

Project Title: Study of the metabolites of epinephrine in human body fluids.

Principal Investigator: Elwood H. LaBrosse

Other Investigators: Seymour S. Kety, Julius Axelrod, and Irwin J. Kopin

Cooperating Units: Unit on Psychosomatics, and Sections on Psychiatry and Physiology

Man Years (calendar year 1960)		Patient Days (calendar year 1960)
Total:	4.00	48
Professional:	1.50	
Other:	2.50	

Project Description:

Objectives: To investigate the metabolites of epinephrine and norepinephrine in the urine and in the blood in the approach to studies of the *in vivo* metabolism of these important neurohumors in normal and mentally ill subjects.

Methods Employed: Normal subjects and schizophrenic patients were infused with 1 mg. of tritium-labeled epinephrine. Urine was collected for 48 hours and the total radioactivity in the urine was assayed. The urine was also examined for metabolites of the epinephrine. This was done by extracting portions of the urine with isoamyl alcohol after adjustment to pH 10. Metanephrine glucuronide was determined by treating the urine with β-glucuronidase before extraction. In addition, an acid hydrolyzable conjugate of metanephrine was found; this conjugate was hydrolyzed by adjusting the urine to 1 N with HCl and heating for 30 minutes at 100°C before extracting. 3-Methoxy-4-hydroxymandelic acid (VMA) was extracted from the urine with isoamyl alcohol after adjusting to pH 1; this compound was found to be free, i.e., unconjugated in the urine. Chromatography on columns of silica gel was also used to separate the acidic metabolites.

Project Description (continued):

The H^3-epinephrine content of blood and plasma has been studied by chromatography on alumina columns. Radioactivity in the eluates has been determined by counting aliquots in the scintillation counter.

3-Methoxy-4-hydroxyphenylglycol (MHPG) was determined by hydrolyzing an aliquot of the effluent from the alumina column using Glusulase. The hydrolyzed solution was passed through a Dowex 50 column, and MHPG was extracted from the salt-saturated effluent with ethyl acetate. 3,4-Dihydroxymandelic acid (DHMA) was determined by elution from the alumina column with 0.2 N sulfuric acid and extraction with ethylacetate.

Patient Material: Twelve male schizophrenic patients and 12 normal male volunteers were used in this study.

Major Findings: The tritium-labeled urinary metabolites of H^3-epinephrine were found to be as follows:

		Normals (12)	Schizophrenics (12)
Epinephrine; unchanged		7%	7%
Metanephrine:	Free	5	6
	Glucuronide	6	9
	Sulfate	30	29
	Total	41	44
3-Methoxy-4-hydroxyphenylglycol		7	9
3-Methoxy-4-hydroxymandelic acid		41	38
Dihydroxymandelic acid		2	2
Total Percent of the urinary tritium accounted for by the above metabolites:		98	100
Percentage of infused tritium excreted in 54 hours:		93	87

Calculations from these data, using known relationships indicate that 65% of the tritium-labeled epinephrine undergoes 3-O-methylation as the first step in its metabolism. This finding is in agreement with previous reports by Axelrod (70%), and with a more recent report by Kopin (67%) using a double-labeling technique. As reported last year, there is practically no difference between the pattern of urinary metabolites in normals and schizophrenic patients. The 7% 3-methoxy-4-hydroxyphenylglycol for the normals and 9% for the schizophrenics is

Project Description (continued):

the only statistically significant difference (P = 0.01), but since the difference is so small, it offers little support for the hypothesis of an altered epinephrine metabolism in schizophrenia.

Significance to Bio-Medical Research and the Mental Health Program: These findings provide factual material for the evaluation of the role of epinephrine in the function of the nervous system under normal conditions and in mental disease.

Proposed Course of Project: To develop methods for the determination of epinephrine and norepinephrine metabolites under various conditions of stress, without the administration of radioactive catechols.

Part B included: Yes

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B: Honors, Awards and Publications

Publications other than abstracts from this project:

1. Axelrod, J.: The metabolism of epinephrine and other sympathiomimetic amines. Physiol. Rev. 39: 751-776 (1959).

2. Kopin, I.J. and Axelrod, J.: Presence of 3-methoxy-4-hydroxyphenylglycol and metanephrine in pheochromocytoma tissue. Nature 185: 788 (1960).

3. LaBrosse, E.H. and Mann, J.D.: Presence of metanephrine and normetanephrine in normal human urine. Nature 185: 40 (1960).

4. LaBrosse, E.H., Axelrod, J., Kopin, I.J. and Kety, S.S.: Metabolism of 7-H^3-epinephrine-d-bitartrate in normal young men. J. Clin. Invest. (in press).

5. LaBrosse, E.H., Mann, J.D. and Kety, S.S.: The physiological and psychological effects of intravenously administered epinephrine, and its metabolism, in normal and schizophrenic men. III. Metabolism of 7-H^3-epinephrine as determined in studies on blood and urine. J. Psychiat. Res. (in press).

Honors and Awards relating to this project:

Dr. LaBrosse was invited to speak at a meeting of the Biochemical Group, of the North Jersey Section of the American Chemical Society, April 1960.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Studies of the interrelationships of the nervous and circulatory systems.

Principal Investigator: P. V. Cardon, Jr., M.D.

Other Investigator: Allen F. Mirsky, Ph.D.

Cooperating Units: Laboratory of Psychology

Man Years (Calendar Year 1960)		Patient Days
Total:	1	50
Professional:	1/2	
Other	1/2	

Project Description:

Objectives: To study changes which occur in the circulatory system in association with changes in various parameters of central nervous system function.

Methods Employed: Circulatory variables are assessed by the following methods: pulse rate, blood pressure, impedence plethysmograph, finger-tip volume plethysmograph, respiratory sphygmograph. Psychological variables are assessed by direct observation, by evaluations done by other workers at NIH, or by the Continuous Performance Test (Dr. Mirsky).

Patient Material: Normal volunteers on 4-W. Schizophrenic patients on 2-W.

Major Findings: Although chlorpromazine may markedly impair responsiveness, the unresponsive state is not accompanied by gross changes in EEG, respiratory pattern, or finger plethysmogram. On the other hand, in the sleep-deprived state, periods of unresponsiveness may be distinguished from periods of responsiveness, on the basis of changes in these physiological variables, with about 85% accuracy. By varying the stringency of the physiological criteria of diminished alertness, it is possible on the one hand to predict correctly a majority of instances of alert behavior without including any instances of unresponsiveness or, on the other hand, to predict about one-third of all instances of unresponsiveness without including any instances of alert behavior.

Significance to Mental Health Research: Any information bearing on the mechanism of action of a drug such as chlorpromazine may have lasting significance to mental health research. The analysis of the data on sleep-deprived subjects reveals enough dependability to encourage one to think that the observations may have immediate applicability to the problem of ensuring alertness during monotonous tasks in which rapid response to infrequent cues is required, particularly in military or space travel situations.

Projected Course of Project: A similar study, administering barbiturates.

Part B included: Yes

Part B.

Publications:

Cardon, P.V. Jr., Sokoloff, L., Vates, T.S., Evarts, E.V., and Kety, S.S.: The physiological and psychological effects of intravenously administered epinephrine and its metabolism in normal and schizophrenic men. I. Effects of heart rate, blood pressure, blood glucose concentration and the electroencephalogram. J. Psychiat. Res. I: 1961 (in press).

Pollin, W., Cardon, P.V., Jr., and Kety, S.S.: The effect on psychiatric patients of loading with various amino acids during chronic iproniazid administration. Science (in press).

Mirsky, A.F. and Cardon, P.V. Jr.: A comparison of the behavioral and physiological changes accompanying sleep deprivation and chlorpromazine administration in man. Submitted to EEG clin. Neurophysiol.

Serial No. M-CS-OC(C)-6
1. Laboratory of Clinical Science
2. Office of the Chief
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: A. Measurement of epinephrine metabolism in the rat by a technique of double labeling.
B. Metabolism of melatonin.

Principal Investigator: Irwin J. Kopin

Other Investigators: C.M.B. Pare, Julius Axelrod, and Herbert Weissbach

Cooperating Units: Section on Pharmacology, LCS, NIMH, and Laboratory of Clinical Biochemistry, NHI.

Man Years (calendar year 1960)		Patient Days (calendar year 1960)
Total:	2.25	None
Professional:	1.25	
Other:	1.00	

Project Description:

Objectives:
A. Using C^{14} and H^3 labeled precursor and intermediates of catechol metabolism, the relative magnitudes of the various pathways of metabolism are being determined using the procedures previously described. The effect of various enzyme inhibitors on these pathways has also been studied.

B. Melatonin, 5-methoxy-N-acetylserotonin, an indole formed from serotonin mammalian pineal gland and found in peripheral nerve as well as that gland, is the most powerful melanocyte contracting substance encountered. The metabolism of this interesting substance has been investigated using melatonin labeled in various positions with C^{14} or H^3.

Methods Employed:
A. 1. Synthesis of metanephrine-methoxy-C^{14} by enzymatic methods.
2. Animal experiments: Rats are injected intravenously with a mixture of epinephrine-7-H^3 and metanephrine-methoxy-C^{14} in a known ratio. The urine is collected at intervals and the

Project Description (continued):

H^3/C^{14} ratio in the various metabolites determined. The ratio of H^3/C^{14} in the metabolites may be used to determine the importance of each pathway in its formation. Other C^{14} and H^3 compounds will be used in similar experiments.

B. Melatonin methoxy C^{14}, 2-C^{14}, or acetyl H^3 was synthesized using organic chemical or enzymatic means and administered to rats. After collection of the urine and bile, the various radioactive constituents were separated by paper chromatography and attempts made to identify the metabolites. Mice injected intravenously with melatonin acetyl H^3 were sacrificed at various time intervals and the disappearance curve of melatonin in the whole animal determined. The various organs of rats receiving melatonin-acetyl H^3 were analyzed for total radioactivity and melatonin.

Major Findings:

A. 1. A new metabolite of epinephrine, 3,4-dihydroxyphenylglycol, has been identified. This metabolite constitutes an intermediate in the formation of 3-methoxy-4-hydroxy-phenylglycol from epinephrine when deamination of epinephrine occurs prior to methylation.

2. Metanephrine may be demethylated to epinephrine, in vivo.

3. An estimate of the importance of the pathways of epinephrine metabolism in rats has been made. About 2/3 of an injected dose of epinephrine undergoes methylation while the rest is either excreted as such or acted upon by monoamine oxidase. About half of the 3-methoxy-4-hydroxyphenylglycol and 3-methoxy-4-hydroxymandelic acid formed from injected epinephrine is formed by methylation followed by deamination.

B. Melatonin is distributed to all tissues including the brain. It is rapidly and completely metabolized, mostly by 6-hydroxylation, and the 5-methoxy-6-hydroxy-N-acetylserotonin excreted in the urine and bile mostly as the ethereal sulfate but in small part as the glucuronide. Another non-indolic metabolite accounts for about 12% of injected melatonin in the rat.

Significance to Biomedical Research and the Mental Health Program: Abnormalities in catecholamine or indole metabolism have been implicated in schizophrenic as well as in anxiety states and various psychosomatic disorders. An understanding of the metabolism of these substances is essential to the understanding of any of these abnormalities.

Project Description (continued):

Proposed Course of Project: The effects of various states--hypertension, hyperthyroidism, etc. and of various drugs, e.g. marsilid, chlorpromazine, etc., on the metabolism of the catecholamines will be investigated. Attempts will be made to investigate the physiologic role of melatonin.

Part B included: Yes

Part B: Honors, Awards, and Publications

Publications other than abstracts from this project:

Kopin, I.J. and Axelrod, J.: 3,4-Dihydroxyphenylglycol, a metabolite of epinephrine. Arch. Biochem. Biophys., 89: 148, 1960.

Kopin, I.J., Pare, C.M.B., Axelrod, J. and Weissbach, H.: 6-Hydroxylation, the major metabolic pathway for melatonin. Biochim. Biophys. Acta, 40: 377-378, 1960.

Serial No. M-CS-OC(C)-7
1. Laboratory of Clinical Science
2. Office of the Chief
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Role of the central nervous system in fat metabolism.

Principal Investigator: P. S. Mueller, M.D.

Other Investigators: P.V. Cardon, Jr., M.D., Marian W. Kies, Ph.D., F. Solomon, M.D. (Adult Psychiatry), J. Fishman, M.D. (Adult Psychiatry), and D. Horowitz, M.D. (NHI).

Cooperating Units: Section on Biochemistry, LCS, Laboratory of Adult Psychiatry, and GMET Branch, NHI.

Man Years: (Calendar year 1960)		Patient days
Total:	2	200
Professional:	1 1/2	
Other:	1/2	

Project Description:

Objectives: To study the nature of psychic phenomena which influence fat metabolism, and the operative mechanisms.

Methods Employed: Plasma free (unesterified) fatty acids (FFA) are measured under a variety of circumstances in man and animals. Circumstances include fasting, chronic caloric deprivation or over-load, chronic exercise, insulin administration, vitamin C deprivation, experimental allergic encephalomyelitis, administration of heparin, hypnotic induction of various affective states, spontaneous clinical depressive states, administration of nicotine and of various compounds related to epinephrine and norepinephrine.

Patient Material: Normal volunteers on 4-W, 4-E, and in NHI. Schizophrenic patients on 2-W. Selected patients of Laboratory of Adult Psychiatry.

Major Findings:

1. Volunteers were studied as to FFA changes during fasting over a 38 hour period. With a dietary intake of 30 to 60 calories per kilogram body weight per 24 hours prior to fasting, the patients maintained a constant relatively low FFA (below 0.58 in Eq/L) for 18 to 22 hours of fasting. Then between 18 to 22 hours after the start of fasting, a sigmoid increase in FFA occurred over the course of two hours to a concentration around 0.90 mEq/L. This abrupt rise can be made to occur earlier if calories are restricted for a week preceding the fast, but is not delayed by caloric excess.

2. The scorbutic guinea pig is unable to elevate FFA similarly in response to fasting. He does have a small but significant increase in his 5 hour fasting FFA concentration as compared to normal, but at 29 hours of fasting he has the same concentration of FFA as at 5 hours fasting, while the normal animal has a doubling of his FFA. Injection of vitamin C into scorbutic guinea pigs restores FFA to normal within 29 hours.

3. A study in conjunction with Dr. Marian Kies found marked increases in FFA in guinea pigs suffering from experimental allergic encephalomyelitis (EAE). When the animals were made scorbutic EAE was entirely prevented. On restoring the normal diet after three weeks, the guinea pigs remained resistant to the first and to a repeat innoculation of the EAE injection. Increases in FFA were found to correlate well with the disease index developed independently by Dr. Kies, and to occur much more frequently than the visible plasma lipemia noted previously by Dr. Kies.

4. FFA was measured in schizophrenic and normal patients before and after insulin injection. It was found that normal and schizophrenic subjects had identical FFA means as a group before insulin. However, after insulin, approximately one-half of the schizophrenic group deviated significantly from normal. All of the normal patients had falls in FFA after insulin to within a very narrow range. A number of schizophrenic patients consistently had either rises in FFA after insulin or falls of small magnitude to a concentration above the normal range. A significant consistency was found among the individual schizophrenic patients as to FFA concentration after insulin and as to type of response after insulin.

5. In collaboration with Dr. David Horowitz, Section on Experimental Therapeutics, NHI, it has been found that dopamine is unable, within physiologic ranges, to stimulate increases in FFA. Nicotine intravenously and by cigarette gives none or only minimal reaction.

6. A study in collaboration with Dr. Frederic Solomon, Adult Psychiatry Branch, NIMH, attempted to correlate increased FFA concentrations with embryomegaly. In diabetes and in obesity embryomegaly has been observed clinically and in animals. Increased FFA has also been reported in diabetes and in obesity. A number of pregnant rats were injected daily with heparin and fed normal or high lipid diets in attempt to reproduce embryomegaly experimentally. No significant increase in fetal size could be shown.

7. The collaborative studies with the Adult Psychiatry Laboratory on hypnotically induced and spontaneous affective states are too recent for reportable results.

Significance to Mental Health Research: Most of the studies summarized might be placed in the somewhat paradoxical category of "basic clinical research." The nature of the clinical problems to which they might eventually prove pertinent can only be speculated upon. They include schizophrenia, depressive states, neurasthenia, obesity, atherosclerosis, and diseases involving auto-immune mechanisms.

Proposed Course of Project: Pursuit of the leads developed.

Part B included: Yes

Part B.

Publications:

Mueller, P.S. and Cardon, Jr., P.V.: Plasma Free Fatty Acids in Fasting Vitamin C Deprived Guinea Pigs. J. Lipid Research (in press) Jan. 1961.

Mueller, P.S.: Plasma Free Fatty Acid Concentrations (FFA) in Schizophrenia Before and After Insulin Stimulation. Submitted to the J. of Psychiatric Research.

Serial No. M-CS-OC(C)-8
1. Laboratory of Clinical Science
2. Office of the Chief
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A:

Project Title: The effect of 5-HTP on the psychotomimetic properties of LSD in man.

Principal Investigator: C. M. B. Pare

Other Investigators: Elwood H. LaBrosse

Cooperating Units: None

Man Years (calendar year 1960)		Patient Days (calendar year 1960)
Total:	0.50	140
Professional:	0.40	
Other:	0.10	

Project Description:

Objectives: Lysergic acid diethylamide (LSD) antagonizes the peripheral actions of serotonin; the hypothesis has been advanced that the CNS effects of LSD also involve its interaction with serotonin. A double blind study was designed to explore this hypothesis.

Methods Employed: The plan of the study was as follows:

1. Base line levels were obtained on each experimental day by making a clinical evaluation and administering the psychological tests before any drugs were given.
2. Subjects were injected intravenously with either saline or 5-HTP--neither the subjects nor the physician making the clinical evaluations were told the nature of this injection.
3. The subjects were given psychological tests 1/2 hour after the first injection.
4. One hour after the first injection the subjects were given the LSD (about 50 μg) intravenously.
5. Clinical evaluation was made and psychological testing was done 1/2, 1 and 2 hours after the LSD.

Patient Material: Seventeen normal volunteers were used in this study, four of which had to be rejected because they developed gastrointestinal symptoms at a low dosage of 5-HTP, of the remaining 13, 9 were female.

Project Description (continued):

Major Findings: The clinical evaluation was correct in selecting which of the times the subjects were pretreated with 5-HTP in the case of 9 subjects and wrong in 4. The symptom questionnaire showed fewer symptoms following 5-HTP in 9 subjects, more symptoms in two subjects and in two subjects the scores were equivocal. These results are significant at the $P = 0.05$ level. The results on the Mood Scale were not significantly different between the 5-HTP and the saline pretreatments.

These results provide limited support for the hypothesis that 5-HTP pretreatment decreases the effect of LSD. If larger doses of 5-HTP could have been given without producing significant side effects, the results may have been more definitive.

Significance to Biomedical Research and the Mental Health Program: A knowledge of the mechanism of production or prevention of LSD effects on the central nervous system would be of considerable value as a tool in developing an understanding of spontaneous psychosis.

Proposed Course of the Project: In view of the equivocal results, and Dr. Pare's return to England this project will be terminated.

Part B included: No

Serial No. M-CS-M(C)-2
1. Laboratory of Clinical Science
2. Section on Medicine
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Effect of certain psychotomimetic drugs on typical and atypical human serum cholinesterase

Principal Investigator: Franklin T. Evans

Other Investigator: Roger K. McDonald

Cooperating Units: None

Man Years (Calendar year 1960)

Total:	5/8	Patient Days
Professional:	5/8	0

Project Description:

Objectives: To compare the cholinesterase inhibiting properties of a number of psychotomimetic drugs using human sera. In addition, to study the effects of some of these drugs on atypical human serum cholinesterase activity.

Methods Employed: The rate of hydrolysis of benzoylcholine by human serum has been studied by various modifications of the method of Kalow and Genest (Canad. J. Biochem. & Physiol. 34:339, 1957). The effect of a number of psychotrophic drugs, mainly psychotomimetic, on this hydrolysis rate has been determined.

Patient Material: Blood samples from normal volunteer subjects, a subject having atypical serum cholinesterase, and from patients with a variety of diseases have been studied.

Major Findings: Among the drugs studied, cholinesterase inhibiting capacity was found not to correlate consistently with psychotomimetic activity. A comparison of the typical and atypical serum cholinesterases with respect to relative inhibition by some of these drugs has shown the atypical form to be less affected than the typical with all compounds studied. However, the magnitude of this difference between the two forms of cholinester ase varies with the particular inhibitor substance used.

Lysergic acid diethylamide and bromlysergic acid, both potent inhibitors of human serum cholinesterase, do not conform to any of the previously reported patterns of differential effectiveness against the two forms of human serum cholinesterase, suggesting a difference in site of action from that seen with other common inhibitors.

Significance to Mental Health Research: Although the physiologic substrate of serum cholinesterase is at present unknown, accumulating evidence indicates that enzymes of this type are involved in maintaining and regulating nervous activity.

In addition, the previously identified abnormal enzyme presents a prototype of a specific, generally benign biochemical peculiarity which results in a dramatically altered response to a specific pharmacologic stimulus (i.e. succinylcholine). This suggests the possibility that other similar abnormalities might alter responsiveness to endogenous rather than exogenous agents. Theoretically, at least, one would expect such an abnormality to result in abnormal behavior patterns.

Part B Included: Yes

Publications:

Evans, F.T. The effect of several psychotomimetic drugs on human serum cholinesterase. Psychopharmacologia 1, 231-240, 1960.

Serial No. M-CS-M(C)-5
1. Laboratory of Clinical Science
2. Section on Medicine
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: A study of urinary excretion of 3-methoxy-4-hydroxymandelic acid in man.

Principal Investigators: Roger K. McDonald and Virginia K. Weise

Other Investigators: None

Cooperating Units: NIH Wards 2-West, 3-East, 3-West, and 4-West. The George Washington University Hospital, Ward 6-B.

Man Years: (calendar year 1960):

Total:	4 7/8	Patient Days
Professional:	1 3/8	330
Other	3 1/2	

Project Description:

Objectives: To study the endogenous release of epinephrine and norepinephrine by measuring the urinary excretion of one of the major metabolites of these catecholamines, 3-methoxy-4-hydroxymandelic acid (VMA). Specifically, to study the excretion of this compound in the following types of subjects and under the following conditions:

1. Nonschizophrenic male and female subjects and male, chronic schizophrenic patients under normally existing conditions.

2. Nonschizophrenic and schizophrenic male subjects before and after the administration of reserpine and chlorpromazine.

3. Nonschizophrenic subjects given certain other psychotrophic drugs.

4. Depressed subjects before and after electroshock therapy.

Methods Employed: The method recently developed in this laboratory has been used to determine urinary VMA. It involves use of radioactive tracer, ion exchange isolation of the VMA from other urinary phenolic acids and subsequent measurement of the metabolite in the purified fraction.

Patient Material: Male schizophrenic patients and nonschizophrenic male and female volunteers hospitalized at the NIMH. Depressed patients admitted to the George Washington University Hospital for electroshock therapy.

Major Findings:

1. Normal male subjects excrete more VMA/24 hours than do normal female subjects. However, when VMA excretion is related to body weight or to creatinine excretion, there is no sex difference.

2. The 24 hour VMA excretion of the chronic schizophrenic group is no different from that of the male control group.

3. A significant diurnal variation in VMA excretion is seen in the nonschizophrenic male subjects studied, the rate of excretion being greater during both the first and second halves of the day than during the night. The schizophrenic subjects have a higher rate of VMA excretion during the first half of the day than during the night.

4. A single parenteral injection of reserpine causes an increase of similar magnitude in urinary VMA in both the control group and the schizophrenic group.

5. Oral administration of chlorpromazine to the nonschizophrenic male subjects causes decreased excretion of VMA. The VMA responses of the schizophrenic subjects to chlorpromazine administration are less consistent, ranging from increases to large decreases. However, the mean response of this group is the same as of the nonschizophrenic group.

6. The effects of the following drugs on urinary VMA have been determined in a group of normal male subjects: Morphine sulfate (16 mg) causes a decrease in rate of VMA excretion during the first 8 hour period following its administration and an increase during the succeeding 8 hour period. The administration of 15 mg amphetamine caused a decrease in urinary VMA in the majority of the subjects tested, as did the administration of 200 mg pentobarbital. Meprobamate (800 mg) administration has no effect on urinary VMA.

7. An initial electroshock caused increased excretion of VMA in 5 of the 7 depressed patients studied. In these 5 patients, the fourth electroshock had no effect or less effect on urinary VMA than the first electroshock.

Inspection of control VMA excretions for nine depressed patients revealed that the involutional depressives (4) had significantly higher values than the other patients and than normal subjects.

Significance to Mental Health Research: 3-methoxy-4-hydroxymandelic acid, a major metabolite of epinephrine and norepinephrine, appears in the urine in 15-20 times the concentrations of the unmetabolized catecholamines. A study of the excretion of this product in normal and disease states, in response to various drugs, and in stressful conditions furnishes valuable information in regard to these hormones which have long been recognized to have significant psychological as well as physiological effects and which, more recently, are being investigated with respect to aberrant metabolism in mental disease.

Proposed Course of Project: Work will continue in this general area in the forthcoming year.

Part B included: Yes

Weise, V.K., McDonald, R.K., and LaBrosse, E.H. Determination of urinary 3-methoxy-4-hydroxy-mandelic acid in man. Clin. Chim. Acta, (in press).

Serial No. M-CS-M(C)-6
1. Laboratory of Clinical Science
2. Section on Medicine
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Studies on Ceruloplasmin

Principal Investigators: Roger K. McDonald and Gary Felsenfeld

Other Investigator: Raymond W. Patrick

Cooperating Units: None

Man Years (Calendar Year 1960)

Total:	7/8	Patient Days
Professional	1/4	0
Other	5/8	

Project Description:

Objectives: The present work on ceruloplasmin is a logical development of the previous study of the possible changes in ceruloplasmin levels in the blood of schizophrenic patients. This study concerns itself with a characterization of the status of the copper atoms in the ceruloplasmin molecule and the relationship of the copper-protein complex to the oxidase activity of ceruloplasmin. Such information is essential to an understanding of the function of ceruloplasmin.

Methods Employed: Oxidized copper is determined by the method of Peterson and Bollier as modified by Angel et al.; reduced copper is determined by the method of Felsenfeld; oxidase activity is determined by a modification of the method of Scheinberg.

Major Findings:

1. Ceruloplasmin normally contains both reduced and oxidized copper.
2. When ceruloplasmin is actively functioning as an oxidase the proportion of the copper which is in the reduced form increases.
3. Oxidation of ceruloplasmin with peroxide results in a loss of the blue color of ceruloplasmin and a parallel loss in oxidase activity. This loss is irreversible. This is in contrast to the reversible loss of blue color of ceruloplasmin associated with reduction by ascorbic acid.
4. Ascorbic acid, in the presence of EDTA, is capable of reducing that fraction of the cupric copper of ceruloplasmin which is directly proportional to the oxidase activity.

Significance to Mental Health Research: The fact that ceruloplasmin levels are elevated in a variety of disease states suggests a physiologic function for this protein. The type of information we are obtaining will be of value in understanding the function of ceruloplasmin.

Proposed Course of Project: Work will continue in this general area of research.

Part B included: No.

Serial No. M-CS-M(C)-7
1. Laboratory of Clinical Science
2. Section on Medicine
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: The determination of creatinine and creatine in urine and plasma.

Principal Investigators: Roger K. McDonald and Virginia K. Weise

Other Investigators: None

Cooperating Units: NIH Wards 2-West, 3-West and 4-West

Man Years:

		Patient Days
Total:	5/8	
Professional:	1/4	26
Other:	3/8	

Project Description:

Objectives: This project is a consequence of the incidental observation that a group of chronic schizophrenic subjects had a lower rate of excretion of creatinine (urine) than a group of male control subjects studied. The object of the present study is to determine whether this difference is related to mental disease or to other factors.

Methods Employed: The creatinine values reported above were obtained using the alkaline picrate method described in "Standard Methods of Clinical Chemistry," Vol. I. Creatinine is now being determined by the specific method of Van Pilsum, et al. (1956) which utilizes the Sakaguchi color reaction. Creatine is being measured by the diacetyl reaction following ion exchange removal of interfering compounds (Krise et al.,1959).

Patient Material: Male schizophrenic patients and nonschizophrenic male volunteers hospitalized at the NIMH have provided subject material for this study.

Major Findings: Using the alkaline picrate method for determining urinary creatinine, it has been found that the normal male subjects studied excrete more creatinine per kilogram of body weight than the chronic schizophrenic subjects. Determination of urinary creatinine in these same urine specimens by the more specific Van Pilsum method has corroborated the difference in excretion rate of this compound between these two groups of subjects.

Significance to Mental Health Research: Any potential metabolic difference between mental patients and nonmental patients should be investigated under carefully controlled conditions using the best available methods.

Proposed Course of Project: Additional mental patients and control subjects will be studied. Emphasis will be placed on the selection of subjects in order to have more nearly matched groups as to age and habitus.

Part B included: No

Serial No. M-CS-P(C)-7
1. Laboratory of Clinical Science
2. Section on Physiology
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Effects of sleep and waking on activity of single neurons.

Principal Investigators: Edward V. Evarts, Peter R. Huttenlocher, Bernard Bihari.

Other Investigators: William T. Burriss

Cooperating Units: None

Man Years (calendar year 1960):		Patient Days
Total:	2 1/2	None
Professional	1 1/2	
Other	1	

Project Description:

Objectives: During the past year, this project has dealt with the effects of sleep and waking on activity of single neurons in visual cortex and brain stem reticular formation. These observations have been made in order to gain further information concerning the nature of sleep.

Methods Employed:

Studies of the activity of single neurons are carried out in unanesthetized unrestrained cats. A small micromanipulator attached to the head of the cat makes it possible to move the microelectrode in such a preparation. Macroelectrodes are also implanted in order to allow recording of spontaneous slow wave activity. Activity is evoked in single neurons by clicks or flashes.

Major Findings:

1. "Evoked and Spontaneous Activity in Single Units of Medial Brain Stem During Natural Sleep and Waking" has been investigated by Dr. Peter Huttenlocher. It was found that units in the reticular formation showed more frequent responses to click stimuli during waking than during sleep. In association with the increased evoked activity during waking, there was a reduction of spontaneous discharge. The results indicate that reduction of evoked activity in the reticular formation during sleep may be the result of occlusion associated with the increase in spontaneous activity.

2. "Effects of Sleep and Waking on Spontaneous and Evoked Discharge of Single Units in Visual Cortex" has been the subject of continuing investigations in the section. Extensive studies of unit responses evoked by retinal photic stimulation have shown that the ratio of evoked to spontaneous activity is greater during waking than during sleep. In addition, it has been shown that the variance of spontaneous discharge rates is greater during waking than during sleep, indicating that there is greater differentiation of spontaneous rate patterns during waking than during sleep. These results emphasize that sleep and waking differ in the pattern of neuronal activity and that sleep is associated with a dedifferentiation rather than with an absence of neuronal activity.

Significance to Mental Health Research: In spite of the gross differences in behavior during sleep as compared to waking, the neurophysiological mechanisms responsible for these differences remain to be elucidated. Elucidation of these mechanisms would seem to be a necessary prelude to the analysis of more complex aspects of behavior.

Proposed Course of Project: Studies of effects of sleep and waking on single neurons in visual cortex and other cerebral regions will continue. It is hoped that these studies will allow the determination of correlations between the functional role of neurons and the effects of waking on their activity. For example, an attempt will be made to discover the relationship between the degree of responsiveness of units to photic stimuli and the effects of sleep on these neurons in the visual cortex.

Part B included Yes

Publications:

Huttenlocher, P.R. Effects of state of arousal on click responses in the mesencephalic reticular formation. EEG clin. Neurophysiol. 1960 (in press).

Evarts, E.V. Effects of sleep and waking on spontaneous and evoked discharge of single units in visual cortex. Fed. Proc. 19: (in press), 1960.

Evarts, E.V., Fleming, T.C. and Huttenlocher, P.R. Recovery cycle of visual cortex of the awake and sleeping cat. Am. J. Physiol. 199: 375-376, 1960.

Serial No. M-CS-P(C)-8
1. Laboratory of Clinical Science
2. Section on Physiology
3. Bethesda, Md.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Studies of evoked potentials in man.

Principal Investigator: Edward V. Evarts

Other Investigators: Robert R. Cox and Edith K. Kessler

Cooperating Units: None

Man Years (calendar year 1960)		Patient Days
Total:	2 1/2	None
Professional	1/2	
Other	2	

Project Description:

Objectives: Studies of cortical electrical activity evoked by peripheral stimuli have been an important means of elucidating the brain mechanisms underlying sensation. The great majority of such studies have been carried out in experimental animals. The present project is designed to study such evoked responses in man. The project is particularly concerned with (1) The Effect of Sleep on Evoked Potentials, and (2) A Comparison of Evoked Potentials in Schizophrenic and Normal Subjects.

Methods Employed: For many years it has been possible to record electrical activity evoked in the cerebral cortex of animals by stimuli such as flashes or clicks. Such recordings are obtained from electrodes placed directly on the exposed cerebral cortex of the experimental animal. Analagous recordings from scalp electrodes in human subjects are not possible because of the distance between such scalp electrodes and the cortical tissue in which the evoked activity originates. Such small signals as do reach the scalp electrodes are masked by the higher amplitude spontaneous cortical activity on which the evoked activity is superimposed. Within the past several years, it has been found that small evoked potentials superimposed on relatively high amplitude spontaneous activity may be detected by averaging a series of responses to an identical stimulus. In such an average, signals which occur at a constant time with respect to the stimulus are enhanced, whereas temporally unrelated electrical activity tends to cancel out.

The methods employed in the present experiment involve the use of averaging as a means of detecting evoked potentials in scalp recordings in man. The instruments employed to carry out the averaging process were developed in this section by Mr. Robert Cox during the past year.

Major Findings:

1. Studies of The Effects of Sleep on Evoked Potentials in Man have shown that level of arousal has marked effects on the configuration and amplitude of cortical responses to flashes of light. During sleep there is an increase in amplitude of the initial components and a reduction in amplitude of the later components of the response.

2. A Comparison of Evoked Potential in Schizophrenic and Normal Subjects has begun, but the results have not yet been analyzed. Preliminary examination of the data fails to indicate any clear differences between the responses of schizophrenic as compared to normal subjects.

Significance to Mental Health Research: The cerebral response evoked by a peripheral stimulus is an index of cerebral electrical activity on the basis of which it will be possible to compare schizophrenic and normal subjects. It seems worthwhile to carry out such a comparison, in spite of the fact that studies of spontaneous electrical activity of the brain have thus far failed to differentiate schizophrenic and normal subjects.

The studies of effects of sleep on evoked electrical activity may provide additional information concerning the neurophysiological processes underlying sleep and waking. Such information will be of considerable value in the design of experiments intended to evaluate the neurophysiological aspects of mental illness.

Proposed Course of Project: Studies of the effects of sleep on evoked potentials will be continued with the aim of determining:

1. Effects of sleep and waking on distribution of evoked potentials throughout the cortex in man.

2. Relationship between evoked potentials and occurrence of dreams.

Studies of evoked potentials in schizophrenic patients will be extended to larger groups of subjects, and will include determination of the distribution of evoked potentials in this group of subjects.

Part B included: Yes

Cox, R.R. and Evarts, E.V. An evoked response detector. EEG clin. Neurophysiol. (in press), 1960.

Serial No. M-CS-Ps(C)-1
1. Laboratory of Clinical Science
2. Section on Psychiatry
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Correlation of Psychiatric Evaluation with Neurophysiological, Psychological and Sociological Evaluation in the Aged.

Principal Investigators: Robert N. Butler, M. D.

Other Investigators: Martha M. Werner; Lillian M. Guerney

Cooperating Units: Section on Cerebral Metabolism, Laboratory of Clinical Science, National Institute of Mental Health; Section on Aging; Section on Social Development and Family Studies; Section on Theoretical Statistics and Mathematics.

Man Years (calendar year 1960):		Patient Days (calendar year 1960):
Total:	1.65	120
Professional:	.60	
Other:	1.05	

Project Description:

Objectives: (1) (a) To select suitable samples of "normal-aged" volunteers and Chronic Brain Syndrome patients for multidisciplinary study. (b) To psychiatrically evaluate and characterize the selected subjects in terms of: diagnosis, psychopathology and modes of adaptation. (c) To correlate psychiatric evaluation with physical status, neurophysiologic (including cerebral metabolism and electroencephalographic measurements) status, and psychological and sociological status. (d) To define (through a, b and c) criteria for the subgroups designated "normal" aged, "senile factor" aged, and chronic brain syndrome. (2) 5-year interval follow-up of the experimental subjects.

Methods: Each subject was interviewed for two 2-hour recorded and observed sessions; the first (Interview A) being an unstructured psychiatric interview, the second (Interview B), a structured interview which includes a mental status examination and inquiry regarding apparent age-relevant concepts. There was systematic rotation in roles of interviewer and observer.

In addition, rating methods were adapted for use by the interviewer, observer and other psychiatrist for independent assessment.

Project Description (Continued):

Methods: Independent and consensus ratings, quantified on a seven-point scale wherever feasible, were made in the following ten categories: (a) Diagnoses, (b) "Age Relevant" Symptoms, (c) Mental Status, (d) Affective State, (e) Psychiatric Symptoms, (f) Separation Response, (g) Concept Evaluation (Disordered Time Sense; Constriction of Future; Age Change Attitudes; Death Concern; Disturbed Body Image), (h) Maternal Attitude Scale, (i) Psychodynamic Formulation, and (j) Interview Behavior Scale. Content analyses of transcribed protocols were performed. Intercorrelational studies, amongst different sections, is proceeding.

Patient Material: 54 medically screened community-resident, male volunteers over 65 years of age.

Major Findings: Nineteen of fifty-four control subjects were free from diagnosable psychopathology. Diagnoses were made for 35 volunteers (65%); for 14 of them there were multiple diagnoses. Included among the primary diagnoses were psychoneuroses, 14 cases; psychoses, 3; and chronic brain syndromes, 2.

Investigations of neurophysiological variables; e.g., cerebral metabolism, in the community aged failed to disclose any simple relationships with psychiatric status (including cognitive defects). But the relationship of reduced cerebral metabolism to the diagnosis of chronic brain syndrome was confirmed. Abnormalities of cerebral circulation and metabolism were also found in a cluster of a group characterized by early senile manifestations. This group which revealed cognitive losses, was found among the nonpsychotic, generally healthy, community-resident aged. "Senile Quality" may be a composite syndrome, a consequence of both organic and psychosocial alterations. This syndrome correlates with psychological tests for "organicity" and probably represents an early stage of Chronic Brain Syndrome.

Investigations of the effects of psychosocial disruptions or losses demonstrates that the personal meaning or psychological significance, of such are more important than the incidence or nature of these stresses, per se. In general, the adaptive or maladaptive function of personality variables or psychopathological features varied with the psychological significance of certain events in the aging experience (e.g., losses; cognitive deficits; forced retirement and the like).

Efforts were directed toward further defining the aging experience of an individual, in terms of intrinsic and environmental changes, and reactions to them.

(a) All subjects described changes. The mean number of changes reported by a subject was 15, the greatest number of these being

Project Description (Continued):

Major Findings: physical changes (mean = 6). Personality-affective, social-psychological and cognitive changes followed.

(b) Changes were not uniformly viewed as deficit in character by the aged subject, as they are so frequently described in the literature pertaining to old age. Changes were often reported as increases or gains in various functions and capacities. Increases were especially described in the personality-affective sphere, where 14 subjects, or 32% reported 100% of these changes as increases, whereas physical and cognitive changes were almost wholly reported as deficits.

(c) Changes were not uniformly viewed as inevitable and unalterable by the aged subject. There was a relationship between the kind of change and the mode of reaction reported. Acceptance was the most frequently reported reaction to physical decreases; compensation was to social-psychological decreases; and both were to cognitive and personality-affective decreases. This mode of Acceptance-Compensation may reflect the selection of and be characteristic of this sample, i.e., healthy and noninstitutionalized.

The adaptive use of psychopathology, the use of activity, the counterphobic attitude, and the function of denial versus insight into the aging experience, are among adaptational modes identified in this group. On the other hand, maladaptation is seen in depression, paranoid isolation, identity loss and the like.

In contrast to other age groups where diagnosis is reasonably predictive of adaptation, in the aged the discrepancy between diagnosis and adaptation seems to be much greater, suggesting a need for revision in assessment and diagnosis in the aged. Evidence was presented suggesting the importance of evaluating the relationship of morale to the nature and effectiveness of adaptive techniques in the contemporary aging experience.

While the representativeness of the sample cannot be claimed a variety of psychiatric, psychosocial and other aspects of these populations are explicitly characterized and thus available for purposes of comparison.

Significance to Mental Health Research: Despite the ever-increasing numbers of aged in this country, until recently the older person himself has been neglected research-wise and there has been much faulty extrapolation of data from other age periods. The study of the normal aged has been especially neglected. The search for adequate evaluation in the aged has its historic roots in the inability to fully understand psychological symptoms on the basis of neuropathological changes. The question as to which are the important parameters for investigation emphasizes the need for a multidiscipline approach. Psychiatric diagnoses run the gamut and may vary from one

Project Description (Continued):

Significance to Mental Health Research: dealing with the individual's personality make-up to defined neurotic symptomatology to organicity; e.g., chronic brain syndrome with arteriosclerosis. Thus the possibility of correlating data with other disciplines is present. A few samples of the theoretical questions posed by one discipline against the data provided by another discipline are as follows: (1) Does the slowing of reaction time postulated by the psychologist as a sine qua non of aging correlate selectively with depression as evaluated by the psychiatrist? (2) Does the diagnosis of chronic brain syndrome with arteriosclerosis formulated as a syndrome by the psychiatrist correlate with evidence of change as measured by the neurophysiologist and internist? (3) Do changes in cerebral blood flow and metabolism as measured by the neurophysiologist correlate with changes in intelligence, perception, etc., as measured by the psychologist and psychiatrist?

With the inception of the follow-up phase, this project becomes the first longitudinal study of the aged. (Mean age of group at first study 71; follow-up 76). The current program is an abbreviated replica of the initial study. It is possible to select those tests and procedures whose reliability and validity were reasonably substantiated in the initial study, to pursue significant findings resulting from the previous investigation, and to test a variety of predictions.

Proposed Course of Project: Follow-up in coordination with the other members of the original multidisciplinary project. Psychiatric interviews of the "normal-control" sample are under way.

Other current work in this project involves preparation of various papers and completion of the volume to be entitled, Aging in Man: A Biological and Behavioral Study. A Research Report of Physiological, Physical, Psychiatric, Psychological and Social Findings in the Normal Aged. This book is scheduled to be published in the spring of 1961.

Part B included: Yes.

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Part B: Honors, Awards and Publications

Publications other than abstracts from this project:

Butler, R. N. and Perlin, S., Depressive Reactions in the Aged: The Function of Denial, Awareness and Insight. (To be published)

Martha M. Werner, Seymour Perlin, M. D., Robert N. Butler, M. D., and William Pollin, M. D., Self-Percieved Changes in Community-Resident Aged: "Aging Image" and Adaptation. (Submitted for publication to Archives of General Psychiatry, American Medical Association)

Honors and Awards relating to this project:

Presentation of methods and findings at International Congress of Gerontology, San Francisco, California, August, 1960.

Serial No. M-CS-Ps(C)-4
1. Laboratory of Clinical Science
2. Section on Psychiatry
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Psychiatric Evaluation of the Effects of l-Epinephrine in a Normal Control and a Schizophrenic Population.

Principal Investigator: William Pollin, M. D.

Other Investigators: Samson Goldin, M. D.

Cooperating Units: Section on Cerebral Metabolism: Louis Sokoloff, M.D.
Unit on Psychosomatics: Philippe V. Cardon, Jr., M.D.
Unit on Schizophrenia: Elwood La Brosse, M.D.
Office of the Chief, LCS: Seymour S. Kety, M. D.

Man Years (calendar year 1960):
Total: 1.00
Professional: .70
Other: .30

Patient Days (calendar year 1960):

Project Description:

Objectives: (1) To investigate the possible role of epinephrine in schizophrenia by (a) studying the effects of a high level of circulating epinephrine upon the schizophrenic disorder; and (b) determining if there is any difference in psychiatric response to a high level of circulating epinephrine between a group of chronic schizophrenics and a group of normal control volunteers. (2) To determine if differences in behavioral response to epinephrine correlate with, and cast any new light on, individual psychophysiological patterns.

Methods Employed: Each experimental subject received l-epinephrine standardized according to body weight infused intravenously at 0.15 micrograms per kilogram per minute. An aliquot of tagged tritiated epinephrine was included in the transfusion. Psychiatric observations proceeded from the time the patient was informed of the procedure shortly before it began through a post-study evaluation period. During each sub-period an interview of approximately twenty minutes duration was conducted. The interview included a portion of the time devoted to unstructured productions by the subject, a standardized symptom check list, brief tests of mental function and, in the case of the schizophrenic population, specific questions pointed at each subject's most prominent psychotic features. The interviews were recorded for further independent analysis. The interviewer and an independent rater made simultaneous

Project Description (Continued)

Methods Employed: observations and ratings. After all 24 subjects had been studied, entire series was reviewed and retrospective rankings made along a number of psychological parameters.

Patient Material: Twelve male normal control volunteers; 12 male schizophrenic patients.

Major Findings: There was no qualitative difference in the psychological response of the schizophrenic and the normal control groups to these infusions. In neither normal control nor schizophrenic subjects did epinephrine cause the appearance or exacerbation of psychotic symptoms. This result fails to support hypotheses which attribute the origin of many of the symptoms of schizophrenia to an abnormal metabolism of circulating epinephrine.

The epinephrine effect was made up of (a) increased arousal, (b) narrowing of the field of attention, (c) a change of direction of attention toward inner body experience, (d) resultant difficulty in communication and some impairment of mental functions.

Subjective feelings of tension accompanying epinephrine were sharply distinguished by a number of subjects from actual life situational anxiety. It is not clear from this study whether the tension noted in and described by these subjects was a primary or secondary effect.

Quantitative differences between the schizophrenics and normal control subjects showed that, as a group, the schizophrenic subjects were much less able to cope with the experimental situation ($P < .002$), showed more anxiety in response to the situation ($P < .02$) but less in response to epinephrine ($P < .02$, and ranked lower on involvement-communication ($P < .02$).

Differences between schizophrenic and normal control subjects in their ability to cope with an experimental situation, and in their resultant situational anxiety, are judged to be widely prevalent in research studies comparing schizophrenic and normal control subjects. Such differences must be given careful consideration before determining that a particular hypothesis being investigated has or has not been demonstrated.

There were marked qualitative differences in the response to the overall situation, and the epinephrine infusion, that cut across the schizophrenic, non-schizophrenic line. Correlations between such differences and biological variables are now being sought. One subgroup of subjects reported the experience in terms of subjectively feeling stronger, more wide awake, more alert. A second subgroup emphasized contrasting feelings: withdrawal, feeling

Project Description (Continued)

Major Findings: weaker, less alert, less wide awake. The "plus" group tended to be composed of subjects who were more related, articulate, expressive and used less denial. The second group tended to be subjects who were initially more withdrawn, and less able to express, or acknowledge their inner experiences.

Significance to Mental Health Research: The possible role of epinephrine or one of its metabolites in the pathogenesis of schizophrenia has received considerable recent interest. The above results help to clarify this role. They suggest a possible indirect contribution to the development of psychosis as a result of the impaired ability to contact the environment which accompanied high circulating levels of epinephrine. They also underline again the great importance of paying considerable attention to factors outside the major experimental variables in any study of schizophrenia.

Proposed Course of Project: Further data analysis, particularly in the area of search for interdisciplinary correlations, is now underway.

Part B included: Yes

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Part B: Honors, Awards, and Publications

Publications, other than abstracts, from this project:

Pollin,W., & Goldin, S., The physiological and psychological effects of intravenously administered epinephrine and its metabolism II. Psychiatric observations. (Submitted for publication to J. of Psychiatric Research)

Serial No. M-CS-Ps(C)-5
1. Laboratory of Clinical Science
2. Section on Psychiatry
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Psychiatric Investigations Within a Multidisciplinary Study of Schizophrenia

Principal Investigators: William Pollin, M. D., R. N. Butler, M. D.,; L. H. Rockland, M. D., S. Szara, M. D.; J. Durell, M. D., L. R. Gjessing, M. D.

Other Investigators: N. A. Schweig, M. D., S. Goldin, M. D., D. Rosenthal, M. D., W. Taylor, Ph. D., C. Schooler, Ph. D., F. Putney, W. Ladusky, P. Blank.

Cooperating Units: Biometrics Branch, Section on Theoretical Statistics and Mathematics; Laboratory of Socio-Environmental Studies; Unit on Psychosomatics, Unit on Schizophrenia, Section on Physiology and Office of the Chief, Laboratory of Clinical Science; Adult Psychiatry Branch, Clinical Neuropharmacology Research Center.

Man Years (calendar year 1960):		Patient Days (calendar year 1960):
Total:	4.55	
Professional:	2.10	1000
Other:	2.45	

Project Description:

A. Amino Acids, and their Derivatives, In Schizophrenia (Pollin,W.)

Objectives: To determine the effects of large quantities of certain amino acids in schizophrenic patients, some of whom were receiving iproniazid.

Methods Employed: There were three time blocks (Periods A, B, and D) during which, in a Latin square design, every patient received in rotation each of the tabulated amino acids (or amino acid combinations) for approximately one week. During Periods C, E, and F the Latin square design was not used. Instead, certain individuals received only one of the substances tabulated, selection depending primarily on their having previously responded to the same, or a related substance. For the most part the L forms of amino acids were given, suspended in chocolate milk, three times daily. The appearance, consistency, and

Project Description (Continued)

Methods: taste of the suspensions were made as similar as possible by adding barium sulfate or flavoring agents as needed.

Behavioral observations were made continuously by nursing personnel. Each patient was evaluated daily by one or more of three psychiatrists. Three additional physicians together examined the patients at weekly intervals, and were the only participants aware of the drug and amino acid regimens. All patients were observed for signs of hepatic disturbance, and serum transaminase was measured each week. No hepatic dysfunction was detected. Electroencephalographic, psychometric, and biochemical studies, which complemented the behavioral and psychiatric evaluations, were also carried out. Nine patients received iproniazid throughout in an effort to increase tissue amine concentration.

Patient Material: A group of twelve chronic schizophrenic patients, carefully screened and previously described. (Ref., "Criteria for the Selection of a Small Group of Chronic Schizophrenic Subjects for Biological Studies," Perlin, S., M. D. and Lee, A. R., M. C., Amer. J. of Psychia. 116:3, Sept. 1959)

Major Findings: a) Marked behavioral changes occurred with l-methionine loading in 4 of the 9 patients receiving iproniazid--in 2 patients on each of 3 trials, in 1 on 2 of 3 trials, and in 1 on 1 of 2 trials. The major clinical features in these patients were: an increasing flood of associations often reaching "word salad;" increasing anxiety approaching or reaching panic; increasing tension and motor activity; depression accompanying a brief period of sharply increased insight; an upsurge of hallucinatory activity; brief intermittent periods of disorientation at the height of agitation.

b) During the higher dose of iproniazid, tryptophan administration was accompanied by mild to marked changes characterized primarily by mood elevation, increased involvement and outgoingness, an early and transitory phase of somnolence, and more active deep tendon reflexes.

c) There was no overlap between marked methionine and tryptophan reactors.

d) Some of the patients, while receiving the higher dose of iproniazid, were given 5-hydroxytryptophan or l-dopa in gradually increasing daily intravenous dosage up to 108 mg. Nausea, abdominal discomfort or vomiting occurred in association with the higher doses of 5-hydroxytryptophan, and transitory hypertension, brachycardia and ventricular extrasystoles with l-dopa. Neither of these substances nor the other amino acids administered altered behavior in a manner detectable clinically.

Project Description (Continued)

Significance to Mental Health Research: Recent reports have indicated that certain amino acids or their endogenous derivatives may affect mental state and behavior, and have led to hypotheses of their involvement in the pathogenesis of some forms of schizophrenia. These findings amplify such previous reports and suggest further lines of investigation.

Proposed Course of Project: Further studies will be planned, directed toward clarifying the extent, significance and mechanisms involved in the observed phenomena.

B. Psychological Effect and Metabolism of N.N. Diethyltryptamine (L.H. Rockland, M. D.)

Objectives: a) To provide information on the relationship between the intensity of the psychological effect and the metabolism (especially 6-hydroxylation) of the drug; and b) to compare the 6-hydroxylating ability of acute and chronic schizophrenic patients with that of normals.

Methods Employed: Each subject receives 60 mgr. of N.N. Diethyltryptamine orally after a psychiatric evaluation. The evaluation includes a routine interview plus scoring the subject on a symptom check list (Jarvik) and on the Rockland scale. The psychiatric evaluations are repeated thirty minutes and ninety minutes after administration of the drug. Urine samples are collected prior to drug administration, and for the nine hours following the drug. The urines are used for determination of 6-hydroxy-diethyltryptamine, and 6-hydroxy skatole.

Patient Material: The group of 14 chronic, male schizophrenics presently on Ward 2-West; a group of acute schizophrenics to be admitted; and the normal control subjects on Ward 4-West.

Major Findings: None as yet.

Significance to Mental Health Research: 6-hydroxylation is a possible route by which psychotomimetic agents might be produced within the human body. Therefore, knowledge of this metabolic pathway, of its relationship to behavioral changes, and particularly of the difference in 6-hydroxylating ability between normal, and chronic and acute schizophrenic patients, is of extreme interest.

C. Periodic Catatonia (Jack Durell, M. D.)

Objectives: To clarify the nature of this reported syndrome by locating and studying a small group of patients meeting the criteria for its diagnosis.

Project Description (Continued)

Methods Employed: In cooperation with Dr. Liev Gjessing, who has played a major role in defining this syndrome, to revue the literature concerning it and locate a patient group who meet the clinical criteria. After clinical study of such a group here, to plan and carry out an appropriate program of psychophysiological studies.

Patient Material: Screening is now underway at Spring GroveState Hospital, St. Elizabeths Hospital and Chestnut Lodge Sanitarium.

Significance to Mental Health Research: As described in the literature, periodic catatonia is a syndrome offering unique research opportunities in the study of schizophrenia and psychotic behavior. This is due to the reported predictability of moves into and out of psychosis, the concurrent physiological changes, and reputed availability of an effective pharmacological therapy: thyroid hormone. Confirmation of these reports, and extension of these findings could provide a substantial new avenue for study of psychophysiological aspects of psychosis.

Part B included: Yes

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Part B.

Publications other than abstracts from this project:

1. Pollin, W., Cardon, P.V.,Jr., & Kety, S.S., Effects of amino acid feedings in schizophrenic patients treated with iproniazid. To be published in Science.

Serial No. M-CS-Ps(C)-6
1. Laboratory of Clinical Science
2. Section on Psychiatry
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Family History and Schizophrenia

Principal Investigators: William Pollin, M. D.

Other Investigators: Jack Durell, M. D., Lawrence H. Rockland, M. D., Noel A. Schweig, M. D., Martha M. Werner, Charlotte Wilkie.

Cooperating Units: Springfield State Hospital, Spring Grove State Hospital of Maryland, St. Elizabeth's Hospital, Washington, D. C., Arlington County Juvenile Court, Virginia, Montgomery County Juvenile Court, Maryland, Psychiatric Youth Services of the Montgomery County Department of Health, Maryland State Training School for Boys, Edgemeade Youth Center, Olney, Maryland.

Man Years (calendar year 1960):
Total: 2.30
Professional: .75
Other: 1.55

Patient Days (calendar year 1960): 476

Project Description:

Objectives: To determine how differences in life history events, and in patterns of family relationships, are related to the occurrence, course, or clinical picture of schizophrenia.

Methods Employed: Comparison of the life course of a schizophrenic patient, and a selected nonschizophrenic sibling, is the basic approach.

A pilot study, utilizing primarily patients on 2-West, and their families, was done. After a period of protracted patient evaluation on Ward 2-West all available material relevant to the family (patient evaluations, state hospital charts, social service histories, etc.) was reviewed and synthesized. Mother, father, nonschizophrenic sibling and patient were then seen individually and in groups for a series of recorded and observed open-ended interviews. These interviews focused on three major areas: (a) personality evaluation; (b) family dynamics; (c) life history events. Independent, and subsequently consensus, judgments and ratings, based on both initial interviews and

Project Description (Continued)

Methods Employed: subsequent tape analysis, were made by participating psychiatrists.

The present 2nd phase is an extension, using two matched groups, each including fifteen families. In one group, there is one schizophrenic child and at least one nonschizophrenic sibling. In the other, there is one child who is a juvenile delinquent, and at least one other who is not. In addition to methods described above, parents are seen for "blind" interviews, and these interviews analyzed by blind judges: i.e., neither interviewer nor judge know which child is ill, nor which illness is present.

Patient Material: (a) Ten families provided data for the original pilot study. Most of these are families of patients now on 2-West. (b) The two groups of matched families for the current phase are being obtained through the several state hospitals (for families of schizophrenics) and through cooperation of the following courts and social agencies (for families of juvenile delinquents): Arlington County Juvenile Court, Virginia, Montgomery County Juvenile Court, Maryland, Psychiatric Youth Services of the Montgomery County Department of Health, Maryland State Training School for Boys, Edgemeade Youth Center, Olney, Maryland. The families are being matched with respect to age, socio-economic status, sibling order and sex.

Significance to Mental Health Research: Studies of the families of schizophrenic patients have led, within recent years, to the development of a number of stimulating and significant new insights and hypotheses.

Up to this point such studies, at least by implication, predominantly have attempted to define certain characteristics which differentiate between the families of schizophrenics as compared to the families of nonschizophrenics. This project attempts to push further in the same direction and study intra- rather than inter-familial differences with the hope that if such differences can be identified they may further clarify our understanding of this disease process in particular and family dynamics in general.

Family studies in schizophrenia, to the present, have largely limited themselves to describing patterns of relationship and personality thought to be characteristic of the disease. Controlled or matching studies have not been reported. It is hoped the present study may go further as a result of three methodological considerations: (a) by focusing on the question

Project Description (Continued)

Significance to Mental Health Research: of historical event and and relationship differences between a schizophrenic patient and his nonschizophrenic sibling within one family: (b) By simultaneously studying families of juvenile delinquents to see if the differences found are characteristic only of schizophrenia, or instead are also present in families where a different type of psychopathology has developed; (c) By use of blind interviews and judges.

Proposed Course of Project: Interview and analysis data obtained from thirty families described above.

Part B included: No.

Serial No. M-CS-Ps(C)-7
1. Laboratory of Clinical Science
2. Section on Psychiatry
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Studies in Methods and Concepts of Psychiatric and Multidisciplinary Research

Principal Investigator: Robert N. Butler, M. D.

Other Investigators: Lillian M. Guerney, Martha M. Werner, Donald Morrison, Ph.D., Samuel Greenhouse, Ph.D.

Cooperating Units: Biometrics Branch, Section on Theoretical Statistics and Mathematics

Man Years (calendar year 1960):
Total: .40
Professional: .30
Other: .10

Patient Days (calendar year 1960):
None

Project Description:

Objectives: (1) To develop techniques and concepts for the study of certain psychological and psychopathological behavior (such as affective states, ego states, self-image, symptom complexes) and the effects of biological or psychological interventions upon such behavior.

(2) To examine the range of use, the limitations, the relevance and the theoretical foundations of various specific techniques; through the empirical study of the investigative, evaluating and observing processes.

Methods Employed: (1) Extensive, continuing review of the literature concerning methods and concepts in psychiatry. (2) Studies of evaluation in psychopharmacology: (a) Individual case study utilizing drugs of different classes (administered blindly) to study the contribution of host characteristics to manifest response. (b) Study of symptom change following transfer through both direct observation and the use of the Lorr schedule. (3) Methodological aspects of studies of the aged: (a) Adaptation and development of structured interviews, interview techniques and rating schedules in studying the mental status, symptoms and interview behavior of the aged. (b) Observations concerning the advantages, issues and limitations of multidisciplinary research. (c) Development of a combined structured interview-content analysis

Project Description (Continued)

Methods Employed: technique for the measurement of self-change in the aged. (d) Study of variation between psychiatrists in assessing diagnosis, affective states, etc., and the effects of interviewer-observer rotation (Samuel R. Greenhouse, Ph.D.; Donald Morrison, Ph.D.) (4) Methodological aspects of biological studies of schizophrenia: (a) Development of nurse-rated schedules for observing and quantifying that behavior of schizophrenic patients and normal control subjects assumed to be pertinent to conventional psychopathology and experimental control (e.g., variation in physical activity level).

1. Weekly 27-item schedule
2. Reaction to Procedure Form

(b) Study of the observing process involved, and of the reliability, validity and relevance of the schedules developed. (5) Exploratory studies of self-view and ego-states of schizophrenic patients and normal aged subjects. (a) Exploration of self-view and ego-states, utilizing self-oriented cues such as Draw-yourself, Draw-your insides, personal photographs, tape recorded voice, and mirror gazing. b) Collection of observations on a unit which is devoted to biological studies of schizophrenia and is characterized by experimental intrusion: viz., examination of the mental and bodily conditions of schizophrenic patients (who tend to "avoid" environmental experience while involved in various self-or internal experiences). Data pertinent to the meanings of experimental procedures, of being "experimental subjects" and of the effects of "intrusions" upon self - and body-image, depersonalization, etc. are collected.

Major Findings: (1) Evaluation in psychopharmacology: (a) Identification of general factors including characterologically-determined organ symbolism in the manifest response to drugs of differing character. (b) Observation of the phenomenon of symptom change (including reversal) as an effect of hospital transfer in schizophrenic patients; this finding is evidence for the methodological requirement of an equilibration or stabilization period following transfer before undertaking experimental studies. (2) Methodological findings from studies of the aged: (a) Determination of tentative criteria (and underlying methodology) for the diagnosis of early depression. (b) Construction of the "aging image" of a medically-healthy, socially-adapted, nonpsychotic aged group (mean age 71) via combined focused interview-content analysis; there is evidence that this procedure may be a useful instrument in measuring adaptation. (c) Adaptations of the first quantified psychiatric mental status examination for the assessment of the aged. (4) (a) The finding that a basic "core of disagreement" is predictable in any systematic behavioral rating schedule; that the factors contributing to such disagreement are potentially valuable and not to be dismissed through tests of "inter-rater reliability". (b) Decrease in inter-rater agreement is a function of the degree of illness. (5) The self-observations of persons in the process of

Project Description (Continued):

Major Findings: mirror gazing appear to provide exceptionally rich material concerning self- and body-image not ordinarily obtained through usual interview approach.

Significance to Mental Health Research: Methods and concepts of psychiatric research require development from the perspective of the individual relationship between the student and the studied. The investigative, especially the observing, process which is, after all, the basis of various rating scale systems, as well as inferences, requires study per se.

In the absence of specific biological indicators (e.g., in the schizophrenic disorders), the range of use, limitations, the relevance and the theoretical foundations of our various techniques and concepts requires special consideration. It is necessary to select psychological indicators (and find methods for their estimation) as contributory to understanding the nature of disorder and to study changes in response to various interventions. Collaborative study of the self and of ego-states by use of self-orienting cues (e.g., mirror gazing) appears to be a promising approach.

Proposed Course of Project:
Continuation along lines indicated.

Part B included: No.

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Quantification of Mental Status Data from Schizophrenic Patients for IBM Processing.

Principal Investigator: Lawrence H. Rockland, M. D.

Other Investigators: Section on Psychiatry, Laboratory of Clinical Science.

Cooperating Units: None.

Man Years (calendar year 1960):

Total:	.35
Professional:	.30
Other:	.05

Patient Days (calendar year, 1960): 20

Project Description:

Objectives: To quantify Mental Status data for IBM processing and correlation with multidisciplinary data.

Methods Employed: The Mental Status data has been divided into three main categories: (1) General appearance and manner; (2) Affect and mood; (3) Content of thought and thought processes.

Within the three categories are included sixteen continua, all arranged so that zero represents normality and increasing numbers represent increasing degrees of pathology. Each patient is scored on each of the continua which apply; a rating of NR (not ratable) may be used where it is not possible to rate the patient. A total score, obtained by adding the scores of all continua, should then be a meaningful estimate of the "psychoticness" of the patient at the time the rating is made; subscores provide a patient profile.

Patient Material: Fourteen chronic male schizophrenic patients on Ward 2-West and three schizophrenic patients from other Mental Health wards.

Major Findings: After several revisions, the present scale shows high levels of inter-rater reliability on preliminary ratings done concurrently by groups of three, four and five psychiatrists.

Project Description: (Continued)

Significance to Mental Health Research: It will facilitate analysis and correlation of mental status data by use of electronic computers.

Proposed Course of Study: It is planned to have several psychiatrists rate the same patient, in the same interview, using 30-40 schizophrenic patients. Statistical studies will then be run to determine the reliability of the scale as a whole, and of each individual item.

Part B included: No.

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Serial No. M-NC (S.E.)-Ps 3
1. Clinical Neuropharmacology Research Center
2. Section on Psychiatry
3. Saint Elizabeths Hospital

Part A.

Project Title: The use of a Social Contact Matrix in a Chronic Psychiatric Ward.

Principal Investigator: Sheppard G. Kellam

Other Investigators: Jacob B. Chassan

Cooperating Units: Saint Elizabeths Hospital

Man Years: (calendar year 1960)		Patient Days (calendar year 1960)
Total:	0.8	5600
Professional:	0.8	
Other:	None	

Project Description:

Objectives:

The purpose of this project is to devise and test a means of assessing social contact in patients on a psychiatric ward, and to use this method to study the social structure of the ward and its relationship to symptom exacerbation.

Methods Employed:

As mentioned in the last Annual Report, a social contact matrix was devised to allow for objective quantification of the degree of any patient's isolation or social interaction. Patients on the ward were observed for over 200 days in terms of the fluctuation in their number of social contacts, as well as the number of times they were alone when on the ward. Also, a symptom assessment was made on each patient each day and quantified on a 5 point scale. It is planned to correlate each possible patient pair over the 200 days to assess whether some patients' symptoms fluctuate in unison. Next, these pairs will be studied to ascertain the reasons for any such relation. Preliminary data suggest that the social life of the patient contains very strong, specific variables which being about symptom fluctuation.

Patient Material:

28 patients on Ward 2 of the William A. White Building, Saint Elizabeths Hospital.

Part A.

Major Findings:

The Social Contact Matrix was found to be a useful means of deriving the group structure of a ward and a useful way of quantifying isolation. A great deal has been learned about the social system and its relationship to symptom fluctuation.

Significance to Mental Health Program:

Quantification and comparison of changes in social behavior is an important requirement in the study of the effects of therapeutic measures (including drugs) on behavior in a mental hospital setting.

Proposed Course of Project:

The method will continue to be used in Saint Elizabeths Hospital, and in the multihospital study, organized by the Psychopharmacology Service Center.

Part B. Included: Yes [ ] No [x]

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Individual Project Report
Calendar Year 1960

Serial No. M-NC(S.E.)- Ps 7
1. Clinical Neuropharmacology Research Center
2. Section on Psychiatry
3. Saint Elizabeths Hospital

Part A.

Project Title: An Investigation into the Interaction between Drugs and Group Nursing in the Treatment of Chronic Schizophrenics

Principal Investigators: Max Hamilton (Visiting Scientist)
Anthony Hordern (Visiting Scientist)
Francis N. Waldrop (Saint Elizabeths Hospital)
John G. Lofft (Saint Elizabeths Hospital)

Other Investigators: Senior Nursing Personnel, William A. White Service, Saint Elizabeths Hospital

Cooperating Units: Saint Elizabeths Hospital, William A. White Service

Man Years: (calendar year 1960)		Patient Days (calendar year 1960)
Total:	1.5	
Professional:	1.5	14,994

Other: During the 17-week course of the study non-professional assistance involved the full-time participation of 6 nursing assistants and the part-time participation of a large number of student nurses, clerks, occupational therapists, etc. It is not possible to provide an accurate estimate of man years time invested by these personnel (all of whom were employees of Saint Elizabeths Hospital).

Project Description:

Objectives:

The specific aims of the investigation were the following:

1. To compare the effects in chronic schizophrenics of prochlorperazine, trifluoperazine and placebo.

2. To compare the effects of intensive group nursing and social therapy in these patients with ordinary nursing care.

3. To examine the interaction between these two types of treatment.

4. To make preliminary observations on predicted variables.

Part A.

Methods Employed:

126 patients (63 men and 63 women), all suffering from a chronic schizophrenic illness, were selected for this study. These patients were transferred to the William A. White Building, 21 patients being placed on each of 6 wards. Each group of 21 was further subdivided on a random basis into a group of 12 (which received routine nursing care) and a group of 9 (which received intensive nursing and social treatment). Each total group of 21 patients was further divided into 3 groups of 7, one receiving trifluoperazine, one prochlorperazine, and one an inert placebo. The project, therefore, involved a 2 x 3 factorial design; patients in each nursing group received all three medications and patients on each type of medication received both types of nursing care. The medication was administered using a double-blind procedure.

Patients were evaluated by paired physician observers for 18 symptoms of chronic schizophrenia. Behavior in the ward was evaluated according to a 9-item rating scale by paired nurses. Prior to initiation of the project, satisfactory reliability of paired observers in use of the rating instruments was established in all cases. Ratings were completed just prior to institution of medication and again at the end of the 2nd, 3rd, 4th, 5th, 7th, 9th, 12th and 17th weeks. Side effects and medication were recorded regularly by head ward nurses and principal investigators.

The intensive nursing and social treatment programs were devised in collaboration with the nursing staff of the William A. White Building. This included group psychotherapy, occupational therapy, dance therapy, recreational therapy, and a program of ward nursing care utilizing small group techniques which afforded maximum interaction between nursing personnel and patients. Those patients receiving routine nursing care did not participate in the special therapies described above, but had available the minimal nursing care program generally available in large wards with a low nurse-patient ratio.

Patient Material:

All patients participating in this project were long-term residents of Saint Elizabeths Hospital (average duration of hospitalization, 18 years), all were under 65 years of age, and free from evident organic disturbance of the central nervous system. Each had an unequivocal diagnosis of schizophrenia. These patients were selected from the chronic wards of the Hospital and transferred into the William A. White Building for purposes of

Part A.

this project several weeks prior to the initiation of the program. All patients receiving medication had their drugs discontinued several weeks prior to the start of the project and the initial ratings.

Major Findings:

1. Statistically significant results were obtained, using a rating scale for symptoms, but were not found with the rating scale assessing the behavior of patients in the wards.

2. Both drugs were effective (in the doses given), trifluoperazine more so than prochlorperazine, but at the cost of more severe side effects. The effect of both drugs on symptoms was achieved within three to five weeks.

3. The intensive nursing and social treatment alone led to a significant reduction in the symptoms of patients in the male ward, but not in the female ward. This effect was roughly comparable to that achieved by the drugs alone without intensive nursing and social treatment.

4. In the case of the male patients, the effects of the two drugs alone, or of the intensive nursing and social treatment alone, or of a combination of these two categories of treatment, yielded very similar degrees of improvement. Such a result could be described as a "ceiling effect". In the case of the women, the evidence suggested that the moderate treatment due to prochlorperazine could be enhanced by the addition of intensive nursing and social therapy. Trifluoperazine produced greater improvement in women than the other drug when used alone, but the combination with intensive nursing and social therapy appeared to have an inhibitory effect.

5. A description in general terms of the clinical effects of the two drugs under study, without describing the specific circumstances (social, nursing, and milieu effects) in which they were used, was apt to be misleading.

Significance to Mental Health Program:

The principal significance of this investigation lies in its clear demonstration of the potency of non-pharmacological variables in the response of psychiatric patients receiving treatment with neuroleptic drugs. It is suggested that the nursing and social environment must be described and taken into account in assessing the effectiveness (or apparent lack of effectiveness) of the pharmacotherapies in a mental hospital setting.

Part A.

Proposed Course of Project:
This project has been completed.

Part B Included: Yes [x] No [ ]

Part B.

Honors, Awards and Publications:

1. The project was presented in abbreviated form in an exhibit and accompanying booklet (Psychopharmacology, A Pictorial Exhibit: Two Studies in a Mental Hospital Setting, U. S. Department of Health, Education and Welfare, Public Health Service) at the annual meeting of the American Psychiatric Association, Atlantic City, May, 1960. It was also presented by one of the investigators at the Student American Medical Association meeting in Los Angeles, June, 1960. It was most recently presented at the Clinical Meeting of the American Medical Association, Washington, D. C., November, 1960.

A paper is in preparation. The nursing aspects of this project are to be presented, by invitation, by Mrs. Helen K. Sainato (Research Nurse, Saint Elizabeths Hospital) before the Psychiatric Nursing Section of the American Psychiatric Association at its annual meeting in May, 1961, Atlantic City.

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Individual Project Report
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Serial No. M-NC(S.E.)- Ps 8
1. Clinical Neuropharmacology Research Center
2. Section on Psychiatry
3. Saint Elizabeths Hospital

Part A.

Project Title: Tables of Average Rho

Principal Investigator: Wilson L. Taylor

Other Investigators: Ching Fong, a volunteer assistant working without pay; two full-time statistical clerks, one part-time employee; also, several part-time volunteer workers.

Cooperating Units: (for consultation) Professional staffs of CNRC and Biometrics Branch, NIMH.

Man Years: (calendar year 1960)		Patient Days: (calendar year 1960)
Total:	1.3	
Professional:	.5	None
Other:	.8	

Project Description:

Objectives:

To develop sampling distributions for rank-difference correlation coefficients averaged over independent samples with equal N's, and to develop tables of significance for these average rho's at the .01, .02, .05, and .10 levels of confidence, two-tailed. No such tables appear to be accessible anywhere in current statistical literature. It is believed that such tables may be of value to researchers gathering measurements in the form of rankings or of ratings which, upon inspection and tests, appear to be more legitimately treated as ranks than as scores.

Methods Employed:

Exact computation of the probability levels of various possible values of average rho was carried out insofar as appeared feasible. Such computation are apt to be tedious. A method of approximating the exact values was therefore developed. This method involved a way of using a table of random numbers. For a particular N such as 4, the exact frequency was determined for all possible values of rho for one group. To each of these possible values was assigned enough random numbers to equal the proportion with which that value could occur by chance. The same was done for all other possible values. Thus a weighted system of drawing chance values of rho for each group was applied, for example, six times to get random values for six groups. When these six values were averaged, one chance value of average rho for six independent groups of four

Part A.

each could be obtained. This process was repeated enough times so that 800 chance values of average rho had been drawn. These 800 values then were lined up according to size and from the number of times each size had occurred exact probabilities were approximated.

This process was validated in the following fashion. It was applied to situations for which exact values had already been computed. It was found that the distribution arrived at by random drawing did not, by application of the chi-square test for "goodness of fit", differ significantly from the exact distribution. Also, only small sampling errors appeared in the tails. This sampling method of estimating the probabilities of given values of average rho was continued until a large part of a ten times ten matrix was completed.

Because it appeared that when the number of objects in a group and the total number of groups both became large enough, the values of average rho should approach a normal distribution, a formula for computing the probabilities of average rho's (based on large numbers of objects and groups) was developed, mathematically proved, and refined by devising a correction for continuity.

Patient Material:
None

Major Findings:
As above.

Significance to Mental Health Program:
Behavior ratings are widely used in psychiatric and psychological research and in many cases inspection shows that they should be treated as ranks rather than scores. Furthermore, it appears that ranks themselves might be more fully utilized if there were tables like the one now developed available.

Proposed Course of Project:
The findings will be submitted to interested hospital groups for use, test and critique.

Part B Included: Yes [ ] No [x]

PHS-NIH
Individual Project Report
Calendar Year 1960

Serial No. M-NC (S.E.)-Ps 9
1. Clinical Neuropharmacology Research Center
2. Section on Psychiatry
3. Saint Elizabeths Hospital

Part A.

Project Title: Excretion of vanillyl-mandelic acid in depressed psychiatric patients before and after electro-convulsive therapy (ECT).

Principal Investigator: Irwin Feinberg, Virginia Weise, Roger McDonald

Other Investigators: Charles Bohrer, (Saint Elizabeths Hospital)

Cooperating Units: George Washington University Hospital
Section on Medicine, Laboratory of Clinical Science

Man Years: (calendar year 1960)

Total:	0.45
Professional:	0.2
Other:	0.25

Patient Days (calendar year 1960)
Not applicable (G.W. Pts.)

Project Description:

Objectives:

It has been suggested that the levels of circulating catechol amines are of prognostic significance in determining the response of patients to ECT. The present study is aimed at obtaining a more valid estimate of circulating catechol amines and their excretion products than has previously been available under the conditions described. Since only 1-2% of epinephrine and nor-epinephrine are excreted unchanged the measurement of vanillyl-mandelic acid (VMA), (which accounts for 30% of the endogenously produced epinephrine) and nor-epinephrine, is relevant.

Methods Employed:

VMA is determined by the method of Weise and McDonald. Two hour urine specimen are collected before and after the first and fifth shock treatments. Patients are rated for depressive symptoms on admission and 3 months after leaving the hospital.

Patient Material:

Depressed patients admitted to George Washington University Hospital for ECT. Final number approximately 20.

Part A.

Major Findings:

Certain elderly depressed patients were noted to have unusually high levels of VMA before ECT. ECT appears to cause a variable increase in VMA, more pronounced on the first than on the fourth shock treatment. These findings are tentative, since such variables as age and medication received before admission to the hospital have not yet been controlled.

Significance to Mental Health Program:

A reliable relationship between catechol amine metabolism and psychiatric state, including response to electro-convulsive therapy, would be of considerable interest in the understanding of the depressive syndrome.

Proposed Course of the Project:

Collection of specimens will be completed by 1 January 1961. Follow-up interviews of discharge patients will be completed by 1 April, 1961. Analysis of this data will follow.

Part B Included: Yes ___ No x

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Individual Project Report
Calendar Year 1960

Serial No. M-NC (S.E.)- Ps 10
1. Clinical Neuropharmacology Research Center
2. Section on Psychiatry
3. Saint Elizabeths Hospital

Part A.

Project Title: Perception of Velocity in Chronic Schizophrenia

Principal Investigators: Irwin Feinberg, Virgil Carlson

Other Investigators: None

Cooperating Units: Section on Perception, Laboratory of Psychology

Man Years: (calendar year 1960)		Patient Days (calendar year 1960)
Total:	0.25	80
Professional:	0.25	
Other:		

Project Description:

Objective:

Numerous reports have appeared in the literature of distortions of the sense of time in schizophrenia; these reports have been predominantly clinical in nature. The present study is an empirical investigation of performance of chronic schizophrenic subjects on a complex task which requires integration of judgements of velocity and of elapsed time. LSD-25 alters judgements of this type in normal subjects. (Held)

Methods Employed:

The task of the subject is to predict the time of arrival of a rotating line,(which has swept through an aperture of 90 degrees and then disappeared) at target points marked on its projected trajectory. The apparatus used was designed by Dr. Carlson. Patients are tested once weekly in 20 minute sessions for up to 15 weeks, since a preliminary study indicated the appearance of certain augmenting errors with repeated testing. Symptom ratings was carried out by Saint Elizabeths Hospital psychiatrists (Dr. F. N. Waldrop, Dr. J. G. Lofft) who were unaware of the patient's performance in the test situation. EEG records were obtained during the course of the test on two occasions for each patient.

Patient Material:

Chronic schizophrenics(hospitalized for more than 3 years) on the wards of the William A. White Building of Saint Elizabeths Hospital. All diagnostic subgroups were included. Patients with evidence of organic brain disease were omitted. Total number approximately 50.

Part A.

Major Findings:

None at present.

Significance to Mental Health Program:

The finding of a systematic aberration of performance on a task of this type would be of considerable interest for the understanding of the psychological changes present in schizophrenia.

Proposed Course of the Project:

Collection of data will be completed by 1 January 1961. Analysis of the large amount of data obtained will require several months.

Part B Included: Yes [x] No [ ]

Part B.

Honors, Awards, and Publications:

Publication:

Feinberg, I. and Garman, E. M.: Studies of thought disorder in schizophrenia II. Plausible and implausible choices on a modification of the Progressive Matrices Test. Arch. Gen. Psychiat., in press.

Serial No. M-NC(S.E.)- Ps 11
1. Clinical Neuropharmacology Research Center
2. Section on Psychiatry
3. Saint Elizabeths Hospital

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Quantitative Studies of dreaming in hallucinating and non-hallucinating schizophrenic subjects.

Principal Investigator: Irwin Feinberg, Richard Koresko, Frederick Snyder

Other Investigators: None

Cooperating Units: Laboratory of Adult Psychiatry
District of Columbia General Hospital

Man Years: (calendar year 1960)		Patient Days (calendar year 1960)
Total:	0.5	56
Professional:	0.25	
Other:	0.25	

Project Description:

Objectives:

The similarity between dreams and hallucinations has been the subject of varied speculation. Certain neurophysiological theories of hallucinations would predict an increased amount of dream activity in the hallucinating patient. The eye-movement recording technique of Aserinsky and Kleitman has been shown to furnish a valid and highly reliable index of dream activity. This technique was used in our study to estimate amount of dream time during uninterrupted sleep in hallucinating and non-hallucinating schizophrenic subjects.

Methods Employed:

Eye-movement activity was recorded from hallucinating and non-hallucinating schizophrenic subjects sleeping in the same room. Each group of two subjects (hallucinator and control) was studied for 5-10 nights. An attempt was made to secure at least 6 hours of sleeping time each night.

Patient Material:

Recently admitted patients to Saint Elizabeths and District of Columbia General Hospitals were studied (present number 9). An attempt was made to match hallucinating and non-hallucinating patients on such variables as duration of hospitalization, age, sex and education. Within the next few months we hope to add to the study a number of chronically ill patients who have been hallucinating for protracted

Part A.

periods, again with suitable controls.

Major Findings:

Preliminary analysis of the data indicates no differences in total dream time between hallucinating and non-hallucinating subjects, both of whom fall into the range established for normals. Both groups of subjects show evidence of markedly disturbed sleep patterns. The records obtained are being re-evaluated according to a more detailed method of analysis, which may reveal the presence of more subtle differences.

Significance to Mental Health Program:

An increased understanding of the phenomena of hallucinations and of their relationship to dreaming would be of value in mental health research.

Proposed Course of the Project:

Collection of data will be completed by 1 July 1961. Final analysis will require several additional months.

Part B Included: Yes ____ No x

PHS-NIH
Individual Project Report
Calendar Year 1960

Serial No. M-NC (S.E.)- CP 1
1. Clinical Neuropharmacology Research Center
2. Section on Chemical Pharmacology
3. Saint Elizabeths Hospital

Part A.

Project Title: Estimation of Catecholamines in Plasma

Principal Investigator: H. Weil-Malherbe

Other Investigator: Grace Bowles

Cooperating Units: None

Man Years: (calendar year 1960)
Total: 0.3
Professional: 0.1
Other: 0.2

Patient Days (calendar year 1960)
0

Project Description:

Objectives:

To develop a reliable, sensitive and specific method, suitable for the routine assay of plasma.

Methods Employed:

Purification of plasma extracts by chromatographic procedures, followed by fluorimetric estimation.

Material:

Human blood from volunteers.

Major Findings:

Additional purification of extracts could be attained by combining an ion exchange procedure with the chromatography on alumina. Previously this was only possible at a sacrifice in convenience, accuracy and sensitivity; however, these drawbacks have now, for the most part, been eliminated.

Results obtained so far are in agreement with those reported by workers using the trihydroxyindole method. With the ethylenediamine method, however, a fourfold increase in sensitivity is obtained, thus

Part A.

allowing the measurement of concentrations of 10^{-10} (0.1 μg/l.).

Significance to Mental Health Program:

There is an urgent need for a reliable method of estimation of catecholamines in the blood in connection with clinical and pharmacological studies on mental patients.

Proposed Course of Project:

It is proposed to use enzymatic methods as a test of specificity. Incubation of plasma with catechol-O-methyl transferase and its coenzyme should remove the material reacting with ethylenediamine. It is also intended to explore the possibility of converting the catecholamines to O-methylated derivatives labelled with C^{14} in the methyl group.

Part B. Included: Yes [x] No [ ]

Part B.

Honors, Awards, and Publications:

Publication:

Weil-Malherbe, H. The condensation of catechols with ethylenediamine.; Biochim, Biophys. Acta, 40, 351, 1960.

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Individual Project Report
Calendar Year 1960

Serial No. M-NC (S.E.)- CP 2
1. Clinical Neuropharmacology Research Center
2. Section on Chemical Pharmacology
3. Saint Elizabeths Hospital

Part A.

Project Title: Estimation of Catecholamine Metabolites in Urine.

Principal Investigator: E. R. B. Smith

Other Investigators: H. Weil-Malherbe, Viola Epps

Cooperating Units: Part of work done at the request of NASA Space Task Group.

Man Years: (calendar year 1960)

Total:	1.6
Professional:	1.2
Other	0.4

Patient Days (calendar year 1960)

Project Description:

Objectives:
To assess the extent of catecholamine discharge from the quantitative measurement of the principal metabolites excreted in urine.

Methods Employed:
Extracts are to be purified by chromatographic and electrophoretic procedures. For the final estimation fluorimetric or colorimetric techniques are used.

Material:
Urine.

Major Findings:
As envisaged in the last Annual Report a sensitive fluorimetric method for the differential estimation of metanephrine and normetanephrine has been developed. However, attempts at isolating the substances from urine by means of cation exchange chromatography met with unexpected difficulties. When strongly acidic resins were used the substances proved difficult to elute from the column; recoveries, therefore, were unsatisfactory. Moreover, the eluant solution interfered with the fluorimetric estimation. With weakly acidic resins the high salt concentration of urine caused incomplete retention, although elution proceeded smoothly. After unsuccessful experiments

Part A.

with solvent extraction a satisfactory desalting technique using electrodialysis was eventually adopted.

Methods for the estimation of 3:4-dihydroxyphenylacetic and 3:4-dihydroxymandelic acids have also been developed. It is proposed to use the method of von Studnitz (Scand. J. clin. Lab. Invest. 12 Suppl. 48, 1960), for the estimation of 3-methoxy-4-hydroxymandelic acid; equipment for carrying out high voltage paper electrophoresis, as used in this method, is at present on order.

Significance to Mental Health Program:

The methods now available account for the major part of catecholamine metabolites. They thus provide a reliable indicator of sympathetic-autonomic activity.

Proposed Course of Project:

The Section has been approached by NASA Space Task Group with the request to carry out analyses of catecholamines and catecholamine metabolites in urine samples of their personnel. These subjects who are being subjected to unusual stress situations offer a unique opportunity to apply the new methods.

Part B Included: Yes [ ] No [x]

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Individual Project Report
Calendar Year 1960

Serial No. M-NC (S.E.)- CP 3
1. Clinical Neuropharmacology Research Center
2. Section on Chemical Pharmacology
3. Saint Elizabeths Hospital

Part A.

Project Title: Changes of Catecholamine Concentrations in the Brain: the effects of reserpine, phenylisoproplyhydrazine, pyrogallol and 3:4-dihydroxyphenylalanine, alone and in combination.

Principal Investigator: H. Weil-Malherbe

Other Investigators: H. Posner, Grace Bowles

Cooperating Units: None

Man Years: (calendar year 1960)		Patient Days (calendar year 1960)
Total:	0.9	0
Professional:	0.4	
Other:	0.5	

Project Description:

Objectives:
To investigate the synthesis and metabolism of catecholamines in the brain *in vivo* and the effect of various drugs thereon, with particular reference to the intracellular distribution of catecholamines.

Methods Employed:
Rabbit brain was homogenized and divided into particulate and soluble fractions. Catecholamines were isolated and estimated fluorimetrically.

Material:
Rabbit brain.

Major Findings:
The injection of 3:4-dihydroxyphenylalanine (dopa) had surprisingly little effect on brain catecholamines. When, however, one or both of the two enzymes concerned with catecholamine metabolism, monoamineoxidase and catechol O-methyl transferase (COMT) were inhibited by the addition of phenylisopropylhydrazine ("catron") or pyrogallol, respectively, the concentration of noradrenaline and particularly that of dopamine rose. The increase was observed in the particulate and soluble fractions, and was similar in the normal brain

Part A.

and in the brain previously depleted of catecholamines by reserpine. In confirmation of earlier experiments (Weil-Malherbe and Bone, J. Neurochemistry 4, 251, 1959) reserpine caused a more rapid depletion in the soluble than in the particulate fraction. The action of reserpine was inhibited by catron, but not by pyrogallol. Catron alone induced a rise of the noradrenaline concentration in the soluble fraction only, without significantly affecting the concentration of dopamine. Pyrogallol alone had no significant effect, but it potentiated the action of catron as well as of dopa, demonstrating, for the first time, the involvement of COMT in the metabolism of endogenous brain catecholamines.

Significance to Mental Health Program:

The experiments gave information on the comparative importance of the two enzymes, monoamineoxidase and COMT, on the factors limiting the synthesis of catecholamines in the brain and on the mechanism of action of reserpine.

Proposed Course of Project:

The experiments have been terminated and a paper embodying the results is now being prepared.

Part B Included: Yes [x] No [ ]

Part B.

Honors, Awards, and Publications:

Publication:

A preliminary report on part of the findings was given by H. Weil-Malherbe at the Ciba Symposium on Adrenergic Mechanisms, held in London on March 30-31, 1960. The paper is in press in the Proceedings.

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Individual Project Report
Calendar Year 1960

Serial No. M-NC(S.E.)- CP 4
1. Clinical Neuropharmacology Research Center
2. Section on Chemical Pharmacology
3. Saint Elizabeths Hospital

Part A.

Project Title: Study of the Metabolites of Psychotropic Tryptamine Derivatives

Principal Investigator: Stephen Szara

Other Investigators: Frances K. Putney

Cooperating Units: None

Man Years: (calendar year 1960)		Patient Days (calendar year 1960)
Total:	.58	
Professional:	.25	None
Other:	.33	

Project Description:

Objectives:

To identify the metabolites of psychotropic tryptamine derivatives such as N.N-diethyltryptamine, α-methyltryptamine, and allied compounds.

To study the various features of the active metabolites in order to increase the sensitivity and specificity of the quantitative method for the determination of the metabolites in urine.

Methods Employed:

Materials are administered to rats by i.p. injection and the metabolites are studied in the urine both qualitatively and quantitatively.

The diazo reaction of the 6-hydroxy indole derivatives is studied spectrophotometrically in order to achieve higher sensitivity and specificity in determining the metabolites quantitatively.

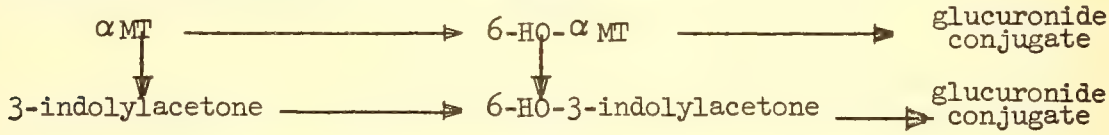
Materials:

Rats, rabbits, cats, monkeys

Part A.

Major Findings:

Similarly to DET and DMT, a third hallucinogenic indole derivative α-methyltryptamine (αMT) is metabolized by 6-hydroxylation both in vitro by rat liver microsomes and in vivo. Since the side chain of αMT is identical with the side chain of amphetamine ($-CH_2.\underset{\underset{CH_3}{|}}{CH}.NH_2$) the compound was also expected to undergo the same microsomal deamination as amphetamine. It was found that αMT is metabolized according to the following scheme:



The quantitative method for determining 6-hydroxydiethyltryptamine (6-HODET) was improved by using diazotized p-amino-benzoic acid ethylester (Benzocain) instead of sulfanilic acid. This permitted to include another cycle of extraction into organic solvent and back into acid which increased the specificity and sensitivity of the method.

Significance to Mental Health Program:

The results underscore the significance of 6-hydroxylation in the metabolism of hallucinogenic tryptamine derivatives.

The improved method is suitable for measuring 6-HDET in human urine after administering DET to the subjects; and, also, in other biological material.

Proposed Course of Project:

A spectrophotometric study is planned to show the specificity of the diazo reaction in acid medium by comparing the characteristics of tryptamine derivatives hydroxylated in the various positions (4, 5, 6 and 7).

The improved method for determining 6-HDET in biological material will be used in studying the distribution of 6-HO-metabolites in the organism, and especially in the brain.

Part B. Included: Yes [x] No [ ]

Part B.

Honors, Awards, and Publications

Publication: Szara, S.: 6-hydroxylation: an important metabolic route for α-methyltryptamine. Experientia (in press)

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Individual Project Report
Calendar Year 1960

Serial No. M-NC(S.E.)- CP 5
1. Clinical Neuropharmacology Research Center
2. Section on Chemical Pharmacology
3. Saint Elizabeths Hospital

Part A.

Project Title: Correlations between Metabolic and Behavioral variables in the study of psychotomimetic tryptamine derivatives.

Principal Investigator: Eliot Hearst and Stephen Szara

Other Investigators: Yvonne Leacock, B. A., Arthur Kales, B. A., and Alice Torovsky, B. A.

Cooperating Units: None

Man Years: (calendar year 1960)		Patient Days (calendar year 1960)
Total:	1.24	
Professional:	.25	None
Other:	.99	

Project Description:

Objectives:

(1) To study the effects of psychotomimetic tryptamine derivatives and their metabolites on several types of behavior in rats, monkeys and pigeons, (2) to correlate behavioral effects with metabolic variables in the same subjects, and (3) to correlate behavioral effects with chemical structure and chemical properties of various tryptamine derivatives.

Methods Employed:

Rat subjects have been trained to depress levers under certain stimulus conditions in order to obtain reward or avoid punishment. Monkeys have been used exclusively on shock-avoidance procedures. Pigeons under hunger drive have been studied in delayed-alternation response situations for food reward. Psychotomimetic tryptamine derivatives were injected intraperitoneally (rats and pigeons) or intramuscularly (monkeys) after the normal, control behavior of these subjects had reached a stable baseline.

Material:

Approximately 15 white rats, 2 rhesus monkeys, and 5 pigeons, who performed their specified responses in standard operant-conditioning apparatus.

Part A.

Major Findings:

(1) Doses of DET (diethyltryptamine) much smaller than those having grossly observable effects in a non-experimental situation have a significant effect on performance. A dose as small as 1-3 mg/kg often was sufficient to bring about a noticeable effect on conditioned responses.

(2) Behavioral threshold doses (mg/kg) for 6-HDET (6-hydroxy DET), the major metabolite of DET, were much lower than for DET in both reward and avoidance situations. When administered in equivalent doses 6-HDET had a much more powerful (though qualitatively similar) effect than DET. This finding indicates that the metabolic product of DET, rather than DET itself, is the critical compound in accounting for the behavioral effects.

(3) Substances closely related in chemical structure to DET and which are 6-hydroxylated like DET (for example, di-methyl-tryptamine or alpha-methyl-tryptamine) have hallucinogenic effects in humans and strong behavioral effects in rats and monkeys, while other structurally-similar substances (e.g. di-hexyl-tryptamine) which are not 6-hydroxylated, have no obvious behavioral effects.

(4) Alpha-methyl-tryptamine, which has been shown to have a much slower rate of 6-hydroxylation than DET, has behavioral effects which are much longer lasting than DET.

Significance to Mental Health Program:

Since relationships among metabolic processes, chemical structure, and behavioral effects of the psychotomimetic drugs are very poorly understood, it is hoped that this joint study will provide a useful technique for attacking cognate problems, in addition to providing important information on the mechanism of action of the specific hallucinogenic agents we are studying.

Proposed Course of Project:

DET, 6-HDET, αMT, DMT and allied compounds are being tested in additional animals in several other behavioral situations. Substances like reserpine and chlorpromazine, which inhibit the metabolism of DET, will be injected in combination with DET to see if the behavioral effects are inhibited as well. In contrast to DET, αMT, etc., tryptamine itself can be found in the brain under normal conditions and is therefore of some additional interest; studies are planned to determine whether tryptamine can be converted into a psychotomimetic agent (which it is not) by pretreatment with other compounds like iproniazid and antabuse.

Part B. Included: Yes [X] No [ ]

Part B.

Honors, Awards, and Publications

Publications: Szara, S., Hearst, E. and Putney, F. Metabolism of hallucinogenic tryptamine derivatives. Fed. Proc., 1960, 19, 23.

Hearst, E. and Szara, S. Correlations between behavioral effects and metabolism of a psychotomimetic drug. Amer. Psychologist, 1960, 15, 476.

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Individual Project Report
Calendar Year 1960

Serial No. M-NC(S.E.)- CP 8
1. Clinical Neuropharmacology Research Center
2. Section on Chemical Pharmacology
3. Saint Elizabeths Hospital

Part A.

Project Title: Metabolism of the Phenothiazine Tranquillizers

Principal Investigator: Herbert S. Posner

Other Investigators: None

Cooperating Units: The Staff of the William A. White Service, Saint Elizabeths Hospital

Man Years (calendar year 1960)		Patient Days (calendar year 1960)
Total:	0.4	
Professional:	0.4	None
Other:	0	

Project Description:

Objectives:
The objective of the project is the further clarification of the pathways of metabolism of the phenothiazine tranquillizers, with special reference to chlorpromazine (Thorazine) and promazine (Sparine).

Methods Employed:
Paper chromatography is used to separate and distinguish the many metabolites of chlorpromazine and promazine. Preliminary evidence for the structural nature of the metabolites has been obtained using differential extraction procedures based on the use of two solvents and three pH values. This combined with the use of β-glucuronidase has led to a useful categorization of the metabolites. Preliminary results have been reported (Posner, H. S., Abstr. Am. Chem. Soc., 81C, Fall 1959). The spots observed are compared with synthetic derivatives in order to make identification.

Patient Material:
Urine of patients normally on phenothiazine tranquillizers is used for these studies.

Major Findings:
Am improved technique of paper chromatography of the phenothiazine metabolites has resulted in more discrete separations of the spots on paper. Using this technique it has been shown that chlorpromazine sulfoxide is apparently a very minor metabolite of chlorpromazine, as found in urine. This finding is in accord with those of two other

Part A.

laboratories. It is very probable, though, that other sulfoxide compounds are present as evidenced by their mode of color development. Evidence of this effect has been presented by another group.

Two phenolic derivatives of promazine were obtained and shown definitely not to represent any of the phenolic promazine metabolites of human urine, either in terms of their R_f value, or their color reaction. Thus, in the case of promazine, only two possibilities for the position of the hydroxyl group in the molecule are left to be considered.

2-Hydroxyimipramine was obtained as a gift of Geigy Laboratories and shown to be identical with one of the phenolic metabolites obtained from the urine of patients receiving imipramine. Imipramine, an antidepressant, is not a derivative of phenothiazine, but of similar enough structure to suggest some similar pathways of metabolism.

Comparison of the products of oxidation of chlorpromazine and some of its derivatives by the iron, ascorbic acid, versene system, with the urinary metabolites, has yielded further information concerning structures of some of the phenolic metabolites. Final identification will be made when synthetic derivatives, which are now being prepared, are received.

Attempted separation of the metabolites on cellulose columns has been successful.

Significance to Mental Health Program:

Further knowledge of the metabolites of the phenothiazine tranquillizers may open the way to further studies on the mechanism of action of these drugs. Since many phenolic amines have been found to possess potent activity on the central nervous system, (i.e. serotonin, norepinephrine, bufotenine, psilocybin, o- and m- tyramine), the possibility exists that phenolic derivatives of chlorpromazine might also possess C.N.S. activity. More important, they might mediate the action of the parent drug. This suggestion however is still entirely hypothetical.

Proposed Course of Project:

As the phenolic derivatives of chlorpromazine are received, they will be compared paper-chromatographically with metabolites found in the urine of patients and animals receiving chlorpromazine. Little work is contemplated on the nature of the non-phenolic metabolites since this has been reported in part by another group. Confirmation of the identity of metabolites and synthetic products will be attempted also by other than paper chromatographic techniques.

Part B. Included: Yes [ ] No [X]

PHS-NIH
Individual Project Report
Calendar Year 1961

Serial No. M-NC(S.E.)- CP 12
1. Clinical Neuropharmacology Research Center
2. Section on Chemical Pharmacology
3. Saint Elizabeths Hospital

Part A.

Project Title: Psychological Effect and Metabolism of N.N-diethyltryptamine

Principal Investigator: Stephen Szara

Other Investigators: Lawrence H. Rockland
David Rosenthal
Leslie Libow
Joseph H. Handlon
Harold Greenberg
Frances K. Putney
Arliene McCamey

Cooperating Units: Laboratory of Clinical Science
Adult Psychology Branch
Laboratory of Psychology
Multidisciplinary Research Unit (3 East)

Man Years: (calendar year 1960)		Patient Days (calendar year 1960)
Total:	2.6	
Professional:	1.8	54
Other:	.8	

Project Description:

Objectives:

The project is intended to provide information on the relationship between the intensity of the psychological effects and the metabolism (especially 6-hydroxylation) of N.N-diethyltryptamine.

The obtained metabolic data in normal volunteers will serve as control in comparing 6-hydroxylation *in vivo* in chronic and acute schizophrenic patients with normals.

Since 6-hydroxylation of indole derivatives is a possible endogenous pathway in the production of psychotomimetic compounds, the question whether or not there is a difference between schizophrenics and normals in their ability to hydroxylate DET is pertinent.

Part A.

Methods Employed:

The pharmacy of the NIH prepares capsules containing the drug and the placebo. The pharmacy has a list of the patients involved. Each receives the drug on one day and placebo on another day. Only the pharmacy knows which substance is being administered on any given day.

DET is given by mouth to volunteers in a capsule and the psychological effect is assessed by two independent observers during a psychiatric interview. Between the two interviews, various psychological tests are administered to measure the change in reaction time, perception, and perhaps concept formation. Blood pressure, pulse rate, respiratory rate, and pupil size measurement are taken regularly to follow the autonomic effects of the drug.

Urine samples are collected before and after the drug is taken and the amount of 6-HDET, the principally active metabolite of DET, is determined in the samples. The amount of 6-hydroxyscatol, a normally occurring 6-hydroxyindole derivative, is also measured before and after the experiment.

Patient Material:

Normal volunteers on Ward 4W (C.C.)
Chronic Schizophrenic patients on Ward 2W
Acute Schizophrenic patients on Ward 3E

Major Findings:

Experiments of double blind design with 10 chronic schizophrenic patients has been completed, and the determinations of the various metabolites are under way. The data will be evaluated only after finishing the whole series of experiments.

Significance to Mental Health Program:

Animal experiments have shown that DET produces behavioral changes through a pharmacologically more potent hydroxylated metabolite. The individual differences in sensitivity to the drug appear related to the individual rate of 6-hydroxylation by various individuals.

The human experiment proposed in this project is designed to provide data whether or not the same correlation between psychological effect and metabolism exists.

Part A.

Any difference in the 6-hydroxylating ability between the normal and schizophrenic group may be particularly relevant.

Proposed Course of Project:

The study will be continued as described under 'Methods'.

Part B. Included: Yes [ ] No [x]

PHS-NIH
Individual Project Report
Calendar Year 1960

Serial No. M-NC(S.E.)-CP 13
1. Clinical Neuropharmacology Research Center
2. Section on Chemical Pharmacology
3. Saint Elizabeths Hospital

Part A.

Project Title: Biochemical and Behavioral Study of the rate of 6-hydroxylation of Tryptamine Derivatives.

Principal Investigator: Stephen Szara and Eliot Hearst

Other Investigators: Frances K. Putney
Arliene McCamey

Cooperating Units: None

Man Years: (calendar year 1960)		Patient Days (calendar year 1960)
Total:	1.33	
Professional:	0.5	None
Other:	0.83	

Project Description:

Objectives:
To study the factors which influence the rate of 6-hydroxylation of Diethyltryptamine (DET) in vitro and in vivo and its relation to the behavioral effects of this compound.

Methods Employed:
Usual biochemical methods are used to study the inhibition of the 6-hydroxylation reaction in microsomes by various agents.

In intact animals, DET is given together with compounds found effective in the in vitro test, and the excreted 6-HDET as the measure of 6-hydroxylation is determined.

In operant conditioning experiments the correlation between the rate of 6-hydroxylation and behavioral effect is studied.

Material:
Rats, rabbits, guinea pigs, cats.

Major Findings:
Microsomal enzyme preparations from rabbit and rat liver hydroxylates the following substrates in the 6-position in decreasing order: DET, Dimethyltryptamine (DMT), Tryptamine, α-Methyltryptamine, Indolylacetone.

Part A.

DET seems to be the best substrate to study the inhibition of this reaction. Among others the following compounds have been found to be effective inhibitors: SKF 525, Chlorpromazine, Reserpine and the higher homologues of DET especially dihexyltryptamine (DHT). The last compound is not hydroxylated but inhibits the reaction competitively.

Studies in intact animals and conditioned reflex experiments on the biochemical and behavioral effect of these inhibitors are in progress.

Significance to Mental Health Program:

Since 6-hydroxylation of indoles is the only known metabolic pathway to produce psychotomimetic derivative from drugs structurally closely related to tryptamine, it is conceivable that 6-hydroxylation of a normally or pathologically occurring indole derivative may play a role in the biochemical production of psychotic symptoms in man.

An effective inhibitor might be the prototype of a new class of therapeutic agents in mental illness.

Proposed Course of Project:

Biochemical and behavioral studies will be extended to prove the point that by inhibitory 6-hydroxylation, the behavioral effects of DET and αMT can be depressed.

Various structural analogs with potential inhibitory properties will be synthetized and tested both in vitro and in vivo.

The metabolism of normally occurring indole derivative will be investigated by using various enzyme blocking agents (Marsilid, Antabuse) in order to produce abnormal and, possibly, psychotropic 6-hydroxy indols metabolically.

Part B. Included: Yes [ ] No [x]

PHS-NIH
Individual Project Report
Calendar Year 1960

Serial No. M-NC (S.E.)-CP 14
1. Clinical Neuropharmacology Research Center
2. Section on Chemical Pharmacology
3. Saint Elizabeths Hospital

Part A.

Project Title: The Effect of Schizophrenic Serum on the Concentration of Catecholamines in the Brain of Rabbits.

Principal Investigator: H. Weil-Malherbe

Other Investigators: N. Waldrop, Grace Bowles, H. Posner

Cooperating Units: Saint Elizabeths Hospital

Man Years: (calendar year 1960)		Patient Days (calendar year 1960)
Total:	0.4	0
Professional:	0.2	
Other:	0.2	

Project Description:

Objectives:
To investigate the reports of Mintz and Walaszek (Fed. Proc. 17, 416, 1958) who claimed that the injection of serum from schizophrenic patients, but not that of normal controls or of non-schizophrenic mental patients, leads to an increase of the concentration of adrenaline and noradrenaline in the hypothalamus and other parts of the rabbit brain.

Methods Employed:
Six rabbits are used in each test, two serving as controls, two being injected with schizophrenic serum and two with normal serum. The rabbits are killed 18 hours after the injections and catecholamines are assayed fluorimetrically in various parts of the brain.

Patient Material:
The schziophrenic patients selected have received no drugs for several months past.

Major Findings:
None so far.

Significance to Mental Health Program:
Confirmation of the claims of Mintz and Walaszek would be of obvious importance for schizophrenia research. It is equally important to dispose of far-reaching claims of this nature, if they are unfounded.

Part A.

Proposed Course of Project:

A total of 30 tests is envisaged during a period of 7-8 months. The biochemists engaged in the project are unaware of the origin of the serum samples.

Part B. Included: Yes [ ] No [x]

Serial No. M-NC (S.E.)- CP 15
1. Clinical Neuropharmacology Research Center
2. Section on Chemical Pharmacology
3. Saint Elizabeths Hospital

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: The Blood-Brain Barrier for Adrenaline and Noradrenaline and Its Response to Drugs.

Principal Investigator: H. Weil-Malherbe

Other Investigators: J. Axelrod, C. Hertting.

Cooperating Units: Section of Pharmacology, Laboratory of Clinical Science, NIMH

Man Years: (calendar year 1960)		Patient Days (calendar year 1960)
Total:	0.2	0
Professional:	0.2	
Other	0	

Project Description:

Objectives:
To evaluate the penetration of adrenaline and noradrenaline into various parts of the brain and into the pituitary gland.

Methods Employed:
Cats are injected or infused intravenously with tritium-labelled adrenaline or noradrenaline. The animal is killed after a varying interval and plasma and tissues are analysed for radioactive amines.

Material:
Cats

Major Findings:

The amounts of radioactive adrenaline or noradrenaline penetrating into most parts of the brain are very small and are probably accounted for by the blood content of the tissue. An exception is the hypothalamus where larger amounts are consistently found. Even here the uptake is slower than in most extracerebral tissues.

Many drugs which block the uptake of noradrenaline by extracerebral tissues, particularly the heart, do not affect the accumlation of radioactive noradrenaline in the hypothalamus. The relative freedom of entry into the hypothalamus therefore seems to be specific for noradrenaline and adrenaline and is not due to the absence of a

Part A.

blood-brain barrier generally.

The pituitary gland takes up circulating noradrenaline rapidly and with great avidity. This uptake, too, is less affected by drugs than that of heart tissue, for example.

Significance to Mental Health Program:

The results suggest that the so-called central effects of adrenaline are either indirect or mediated by the hypothalamus.

Proposed Course of Project:

The project is now nearing completion and the results will be submitted for publication.

Part B Included: Yes [x] No [ ]

Part B.

Honors, Awards, and Publications:

Preliminary reports were presented by invitation at a Symposium on Adrenergic Mechanisms held at the Wellcome Foundation in London on March 28-29, 1960 and at the Fourth International Neurochemical Symposium held at Varenna, Italy, on June 12-17, 1960. Papers are in press in the appropriate Proceedings.

PHS-NIH
Individual Project Report
Calendar Year 1960

Serial No. M-NC (S.E.)- CP 16
1. Clinical Neuropharmacology Research Center
2. Section on Chemical Pharmacology
3. Saint Elizabeths Hospital

Part A.

Project Title: The metabolism of protein-bound amide groups in brain.

Principal Investigator: H. Weil-Malherbe

Other Investigators: Mary Ann Sodd

Cooperating Units: None

Man Years: (calendar year 1960)		Patient Days (calendar year 1960)
Total:	0.7	0
Professional:	0.1	
Other:	0.6	

Project Description:

Objectives:
It has previously been observed (Weil-Malherbe and Drysdale, J. Neurochemistry, 1, 250, 1957) that the protein-bound amide groups of brain slices decrease under anaerobic conditions and in the presence of dinitrophenol without a concomitant increase of free ammonia. It is the purpose of the project to re-investigate this observation and to study the fate of the amide groups which disappear.

Methods Employed:
Incubation of slices from guinea pig brain cortex under various conditions, followed by chemical analysis.

Material:
Brain tissue from laboratory animals, mainly guinea pigs.

Major Findings:
Preliminary experiments have confirmed the earlier observations.

Significance to Mental Health Program:
It has been suggested (Vrba, J. Neurochem. 1, 12, 1956) that the major part of the ammonia formation in brain which accompanies nervous activity is due to the hydrolysis of protein amide groups. If protein-amide groups can disappear without the liberation of ammonia, the interpretation of Vrba's experiments has to be reconsidered.

Proposed Course of Project:
Indefinite.

Part B Included: Yes [ ] No [x]

PHS-NIH
Individual Project Report
Calendar Year 1960

Serial No. M-NC(S.E.)-CP 17
1. Clinical Neuropharmacology Research Center
2. Section on Chemical Pharmacology
3. Saint Elizabeths Hospital

Part A.

Project Title: Validity and Usefulness of Some of the Forrest and Forrest Tests for Phenothiazines in the Urine.

Principal Investigators: Herbert S. Posner, CNRC; James D. Solomon, Saint Elizabeths Hospital.

Other Investigators: Mrs. Viola Epps (technician), and technicians of Blackburn Laboratory, Saint Elizabeths Hospital.

Cooperating Units: The staff of the William A. White Service and Blackburn Laboratories, Saint Elizabeths Hospital.

Man Years: (calendar year 1960)
Total: 0.3
Professional: 0.1
Other: 0.2

Patient Days (calendar year 1960)
None

Project Description:

Objectives:
To follow the excretion of phenothiazine compounds in the urine of patients receiving prochlorperazine and Trifluoperazine and placebo on a double blind schedule, and to assess the validity of two of the Forrest and Forrest tests in current use.

Methods Employed:
Morning urine specimens were obtained from patients receiving phenothiazine medication on a double blind schedule. The Forrest and Forrest Piperazine Linked Phenothiazine Test (Am. J. Psychiat., 116, 549 (1959))and an assay for creatinine were performed on all samples. Urines from patients not receiving phenothiazine tranquillers, and from laboratory personnel were assayed by the above method and that for chlorpromazine (Am. J. Psychiat., 114, 931 (1958)).

Patient Material:
Urine of patients normally on phenothiazine tranquillizers is used for these studies.

Major Findings:
Using the test for piperazine-linked phenothiazines, there were 10 false positive reactions out of 26 urines of the laboratory and office personnel. Of 19 patients who had not received a phenothiazine tranquillizer for at least 6 months, there were 12 false positives. The intensity of the reactions ranged from trace to 3-1/2+. The urines of 4 out of 5 patients receiving placebo as part of a double blind study, consistently yielded positive reactions, with few exceptions, over a period of 3 months. The fifth patient on placebo gave 10

Part A.

false positive reactions out of a total of 77. False positive reactions were still obtained one week after cessation of placebo administration. A spot check of the patients capsules showed that they were indeed receiving placebo.

The false positive reactions were not related to bile in the urine as determined by the Gmelin or Huppert tests for bile pigments, to administration of any one drug, or to sex, age, or race. Neither were they due to the possible excretion of phenothiazine from previous administration, administration of the wrong capsules in the case of the double blind study, nor to contaminated glassware.

The test for chlorpromazine, on the other hand, gave no false positive reactions using urine of 19 of the laboratory personnel and 16 of the patients who had not received phenothiazine tranquillizers for at least 6 months. Studies by Dr. Solomon indicated that color intensity followed amount of drug administered quite reliably.

Significance to Mental Health Program:

Since it was felt desirable to know whether or not patients were actually taking their phenothiazine tranquillizers, a series of tests were developed to estimate urinary excretion of the drugs. These experiments represent a test of the validity of two of the tests proposed. One test has been found to be valid (chlorpromazine test), the other being invalid because of the high percentage of false positive reactions (Piperazine-linked phenothiazine test).

Proposed Course of the Project:

The project has been terminated.

Part B. Included: Yes [X] No [ ]

Part B.

Honors, Awards and Publications:

Publication:

Posner, H. S., and Solomon, J. D., "On the Forrest, Forrest, and Mason Tests for Piperazine-linked Phenothiazines and for Chlorpromazine", submitted for publication to Am. J. Psychiat.

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Individual Project Report
Calendar Year 1960

Serial No. M-NC (S.E.)- CP 18
1. Clinical Neuropharmacology Research Center
2. Section on Chemical Pharmacology
3. Saint Elizabeths Hospital

Part A.

Project Title: Pharmacology, Behavioral Activity, and Clinical Significance of Phenolic Derivatives of Chlorpromazine.

Principal Investigators: Herbert S. Posner, Eliot Hearst, Robert Byck, CNRC, NIMH: George Cosmides, PSC, NIMH; Francis N. Waldrop, Saint Elizabeths Hospital

Other Investigators: None

Cooperating Units: The Staff of the William A. White Service, Saint Elizabeths Hospital

Man Years: (calendar year 1960)		Patient Days (calendar year 1960)
Total:	0.2	
Professional:	0.2	None
Other	0	

Project Description:

Objectives:

The study aims: 1) at a comparison of chlorpromazine and its phenolic metabolites in terms of the pharmacological, behavioral, and clinical effects, and 2) an assessment of the relative importance of the orientation of the hydroxyl group in the hydroxylated chlorpromazine derivatives.

Methods Employed:

Chlorpromazine and its phenolic derivatives will be compared pharmacologically and behaviorally in animals. The final series of tests to be used has not yet been decided. Tests which have been used previously in the case of chlorpromazine are being used as a baseline. An assay will be developed for estimation of the phenolic metabolites in urine. Using this assay, correlations between behavioral effects in animals, clinical effects in humans and formation of hydroxylated derivatives will be sought.

Patient Material:

No patient material has yet been used for this study.

Part A.

Major Findings:

Work has just begun on the determination of baseline values for chlorpromazine for some of the pharmacological tests which will be used. No major findings have been obtained to date.

Significance to Mental Health Program:

This study represents a preliminary attempt to obtain correlations between the metabolism of chlorpromazine and its clinical efficacy, including the so called "side effects".

Proposed Course of Project:

The course of the project will be that outlined under methods.

Part B. Included: Yes [ ] No [X]

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Individual Project Report
Calendar Year 1960

Serial No. M-NC(S.E.)- CP 19
1. Clinical Neuropharmacology Research Center
2. Section on Chemical Pharmacology
3. Saint Elizabeths Hospital

Part A.

Project Title: Studies on the Mechanism of Aromatic Hydroxylation.

Principal Investigator: Herbert S. Posner

Other Investigators: None

Cooperating Units: None

Man Years: (calendar year 1960)		Patient Days (calendar year 1960)
Total:	0.2	
Professional:	0.2	None
Other:	0	

Project Description:

Objectives:

Further elucidation of the mechanism of aromatic hydroxylation using the liver microsomal hydroxylating system as a model. This work is a continuation of studies begun as preparation for doctoral thesis while the principal investigator was a member of the Laboratory of Clinical Biochemistry, NHI. This will be reported along with the previous work.

Methods Employed:

The products of the microsomal hydroxylation of naphthalene and 1,2-dihydronaphthalene were investigated by counter-current distribution and by fluorescence analysis. A role for hydrogen peroxide in the hydroxylation of naphthalene was also sought through the use of added H_2O_2, generated H_2O_2, and the use of catalase, an enzyme destroying H_2O_2. Rabbit liver microsomes were used.

Patient Material:

None

Major Findings:

Although naphthalene has previously been shown to be converted to 1-naphthol and to 1,2-dihydro-1,2-dihydroxynaphthalene in the presence of the liver microsomal system, no evidence could be found for the formation of 1,2-dihydro-1-hydroxynaphthalene (or the 2-hydroxy isomer). Furthermore, when 1,2-dihydronaphthalene was synthesized and incubated with the microsomes, it was shown to form a compound which was neither 1-naphthol nor 1,2-dihydro-1,2-dihydroxy-

Part A.

naphthalene. The nature of the product was not determined. A possible mechanism for the formation of 1,2-dihydro-1,2-dihydroxynaphthalene from naphthalene in which 1,2-dihydronaphthalene would be formed as an intermediary, could thus be ruled out.

Neither H_2O_2 added nor generated, both in the dark, was able to lead to the formation of 1-naphthol or 1,2-dihydro-1,2-dihydroxynaphthalene from naphthalene in the presence or absence of liver microsomes. Furthermore, catalase did not inhibit the formation of either compound when added to the hydroxylating system. Thus tentative evidence has been obtained against the role of H_2O_2 in the hydroxylation of naphthalene.

Dependence of the course of hydroxylation of naphthalene and quinoline on pH was demonstrated.

Significance to Mental Health Program:

There is no immediate application of this work to the mental health program. Hydroxylation, however, is an ubiquitous reaction; knowledge of the mechanism of aromatic hydroxylation might lead to control over some endogenous reactions in man resulting from the metabolism of naturally occurring compounds, foodstuffs, and drugs.

Proposed Course of Project:

No further work is contemplated at the present time.

Part B. Included: Yes [ ] No [X]

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Individual Project Report
Calendar Year 1960

Serial No. M-NC(S.E.)- CP 20
1. Clinical Neuropharmacology Research Center
2. Section on Chemical Pharmacology
3. Saint Elizabeths Hospital

Part A.

Project Title: Specificity of the α-Nitroso-β-Naphthol Test for 5-Hydroxyindoles.

Principal Investigator: Herbert S. Posner

Other Investigators: None

Cooperating Units: None

Man Years (calendar year 1960)
Total: 0.05
Professional: 0.05
Other: 0

Patient Days (calendar year 1960)
None

Project Description:

Objectives:

1) Confirmation of the specificity of the α-nitroso-β-naphthol test (Udenfriend, Weissbach and Clark, J. Biol. Chem., 215, 337 (1955)) for 5-hydroxyindoles.

2) The obtaining of information which might lead to knowledge of the nature of the chromophore, and the mechanism of the reaction.

Methods Employed:

The reaction as described by Udenfriend, Weissbach, and Clark has been applied to a large series of compounds chosen for their potential or actual close structural relationships with indoles or 5-hydroxyindoles. The reaction has also been studied on chromatographic paper using the spray as described by Udenfriend, Weissbach, and Clark.

Patient Material:

None.

Major Findings:

With few minor exceptions, the remarkable specificity of the above test for 5-hydroxyindoles has so far been verified using 22 compounds closely related to 5-hydroxyindoles. There are some differences between reactions obtained in solution and on chromatographic paper.

Part A.

Significance to Mental Health Program:

5-Hydroxyindoles have been implicated, albeit indirectly, in a number of effects of phrenotropic drugs.

Proposed Course of Project:

As other desired compounds become available, their reaction in the above test will be investigated. An extended correlation between structure and reactivity will be sought possibly leading to an explanation of the reaction involved.

Part B. Included: Yes [ ] No [X]

PHS-NIH
Individual Project Report
Calendar Year 1960

Serial No. M-NC(S.E.)- BS 6
1. Clinical Neuropharmacology Research Center
2. Section on Behavioral Sciences
3. Saint Elizabeths Hospital

Part A.

Project Title: A Method of Recording from the Cortex while Maintaining Physiologic Conditions

Principal Investigators: Robert J. Gumnit and Robert G. Grossman (WRAIR)

Other Investigators: None

Cooperating Unit: Department of Neurophysiology
Walter Reed Army Institute of Research

Man Years: (calendar year 1960)

Total:	.05
Professional:	.05
Other:	0

Patient Days: (calendar year 1960)

None

Project Description:

Objectives:
To develop a quick and simple method of maintaining a surgically exposed cerebral cortex in a physiologic state.

Methods Employed:
A concentric ring and plug system made of plastic was devised.

Material:
Cats

Major Findings:
A method that permits a small area of surgically exposed cerebral cortex to be kept in a physiologic state for many hours was developed. The technique has been found to have four advantages. (1) Electrodes maintain their position with respect to the cortex without rigid fixation of the head. (2) Working space about the head is not obstructed by manipulators. (3) Plugs may be rapidly interchanged to carry out various experimental procedures. (4) The preparation can be carried out rapidly under light anesthesia.

Significance to Mental Health Program:
Certain manipulations and preparations necessary for some experiments directed at increasing our understanding of the functioning of the brain are simplified by the above procedures.

Part A.

Proposed Course of Project:

The project is terminated. A paper detailing this method is being prepared for publication.

Part B Included: Yes [x] No [ ]

Part B.

Honors, Awards and Publications:

Grossman, Robert G. and Gumnit, Robert J.: A Method of Recording from the Cortex while Maintaining Physiologic Conditions. In Press: EEG and Clinical Neurophysiology.

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Individual Project Report
Calendar Year 1960

Serial No. M-NC(S.E.)-BS 7
1. Clinical Neuropharmacology Research Center
2. Section on Behavioral Sciences
3. Saint Elizabeths Hospital

Part A.

Project Title: Direct Current Changes in the Auditory Area of the Cat in Response to Auditory Stimulation

Principal Investigator: Robert J. Gumnit

Other Investigators: None

Cooperating Units: None

Man Years: (calendar year 1960)

Total:	.25
Professional:	.10
Other:	.15

Patient Days (calendar year 1960)
0

Project Description:

Objectives:
To examine critically reports of Direct Current shifts occurring in the auditory cortex during auditory stimulation and to subject such phenomena to physiological analysis.

Methods Employed:
A very sensitive Direct Current recording system using nonpolarizable electrodes and an ink-writing oscillograph is employed to record from the cortex of very lightly anesthetized cats subjected to auditory stimulation.

Material:
Cats

Major Findings:
The description of such Direct Current changes by a previous investigator has been confirmed and a method devised of reliably obtaining this phenomenon for more detailed analysis. The changes definitely arise in Auditory Area 1, and show localization within that area varying in a yet to be determined manner with the loudness and the pitch of sound stimulation. The phenomenon has been found to be present only when the animal is under a very light degree of anesthesia and when the cortex is kept in a physiologic state of moisture and temperature.

Part A.

Significance to Mental Health Program:

The Direct Current changes were predicted on the basis of certain psychological experiments and the theory was postulated that they are of fundamental importance in the handling of sensory information by the brain. It is believed that this investigation deals with an area of basic brain physiology.

Proposed Course of Project:

Terminated. A second paper dealing with this material is being prepared for publication.

Part B Included: Yes [x] No [ ]

Part B.

Honors, Awards and Publications:

Gumnit, Robert J.: D. C. Potential Changes from Auditory Cortex of Cat. J. Neurophysiol. (Vol. 23), 667-675, 1960.

PHS-NIH
Individual Project Report
Calendar Year 1960

Serial No. M-NC(S.E.)- BS 12
1. Clinical Neuropharmacology Research Center
2. Section on Behavioral Sciences
3. Saint Elizabeths Hospital

Part A.

Project Title: Intracellular Potentials from Respiratory Neurones in the Brain-Stem of the Cat and the Mechanism of Rhythmic Respiration

Principal Investigator: G. C. Salmoiraghi

Other Investigators: R. von Baumgarten

Cooperating Units: Department of Physiology, University of Goettingen, Goettingen, Germany

Man Years: (calendar year 1960)		Patient Days (calendar year 1960)
Total:	.43	0
Professional:	.33	
Other:	.10	

Project Description:

Objectives:
To obtain information regarding the mechanisms responsible for the periodic arrest of the discharge of inspiratory and expiratory neurones.

Methods Employed:
Recording of electrical potential changes by means of microelectrodes inserted into respiratory neurones in the medulla of anaesthetized, decerebrated, decerebellated, thoracotomized cats artificially respired with pure oxygen.

Material:
Cats

Major Findings:
Recording of intracellular potential changes from respiratory neurones in the lower brain-stem of cats was achieved in eight instances. Seven inspiratory and one expiratory neurones were successfully penetrated.

Membrane potentials of these respiratory neurones ranged from 25 to 70 mV. (45 mV. average). Intracellular potential changes observed were synaptic potentials, action potentials, slow repolarizing potentials (following the fast components of an action potential), slow depolarizing potentials (preceding the onset of an action potential), a slow depolarizing shift developing during

Part A.

the burst of action potentials and, in the case of the expiratory neurone, a slow hyperpolarizing shift during the inspiratory phase.

The potential level at which action potentials were produced by inspiratory and expiratory neurones was not the same throughout the burst of action potentials but shifted in the direction of depolarization as the burst progressed.

Depolarizing synaptic potentials were present throughout the cycle but were more evident during the time in which inspiratory and expiratory neurones produced action potentials. Hyperpolarizing potentials were clearly observable in records from the expiratory neurone during inspiration but could be seen less well in records from inspiratory neurones in the interval between successive bursts.

It would appear that three factors contribute to produce rhythmicity of respiratory neurones; namely, a self-reexciting mechanism within the inspiratory and the expiratory networks of neurones tending to maintain activity within the networks; self-limiting systems tending to limit the frequency and the duration of the discharge; and reciprocal innervation which provides inhibition of one network when the other is active. It is suggested that the increase in the firing threshold as the burst of action potentials progresses plays a major role in periodically bringing the discharge to an end.

Significance to Mental Health Program:

This is part of a program dealing with the ways in which aggregates of neurones in the brain-stem control autonomic functions.

Proposed Course of Project:

The project has been completed. Information obtained in this study will now permit the principal investigator to proceed to: (1) investigate the responses of respiratory neurones in the brain-stem of the cat to pharmacological agents applied through multi-barreled electrodes; and (2) investigate the mechanisms responsible for the activity of respiratory motor neurones in the spinal cord of cats.

Part B Included: Yes [x] No [ ]

Part B.

Honors, Awards and Publications:

Salmoiraghi, G. C. and Burns, B. Delisle: Localization and patterns of discharge of respiratory neurones. J. Neurophysiol. 23: 2-13, 1960.

Salmoiraghi, G. C. and Burns, B. Delisle: Notes on mechanism of rhythmic respiration. J. Neurophysiol. 23: 14-26, 1960.

Burns, B. Delisle and Salmoiraghi, G. C.: Repetitive firing of respiratory neurones during their burst activity. J. Neurophysiol. 23: 27-46, 1960.

PHS-NIH
Individual Project Report
Calendar Year 1960

Serial No. M-NC(S.E.)-BS 13
1. Clinical Neuropharmacology Research Center
2. Section on Behavioral Sciences
3. Saint Elizabeths Hospital

Part A.

Project Title: Localization and Patterns of Discharge of Respiratory Neurones in Carassius Auratus.

Principal Investigator: G. C. Salmoiraghi

Other Investigators: R. von Baumgarten

Cooperating Units: Department of Physiology, University of Goettingen, Goettingen, Germany

Man Years: (calendar year 1960)
Total: .53
Professional: .33
Other: .20

Patient Days (calendar year 1960)
0

Project Description:

Objectives:
To investigate the mechanism/s by which a fish produces and maintains rhythmic respiratory movements and to compare these mechanism/s with those responsible for respiratory rhythmicity in cat.

Methods Employed:
Extracellular and intracellular recording of electrical potentials from respiratory neurones in the medulla oblongata of the goldfish by means of micropipettes.

Material:
Goldfish

Major Findings:
1. Respiratory potentials could be recorded from two relatively narrow strips, one on each side of the brain-stem. Histological studies of the structures from which respiratory potentials were recorded are presently being carried out in the Department of Physiology, University of Goettingen, Goettingen, Germany.

2. Respiratory potentials could be divided into two groups, depending on whether they occurred concurrently with abduction or adduction of the gill covers.

3. Neurones of either group continued to behave rhythmically even when all respiratory movements had been abolished by intra-

Part A.

muscularly injected succinylcholine.

4. Abduction of the gill covers following respiratory motor paralysis did not induce any obvious change in the pattern of discharge of respiratory neurones. Conversely, rapid injection of water into the mouth of the goldfish induced a continuous discharge from members of one population and the arrest of discharge of members of the other population.

5. Cerebellar polarization also could modify the rhythm of respiration, as well as the duration of each burst of action potentials and the number of spikes during each burst.

6. Attempts to record intracellular potentials from respiratory neurones were unsuccessful, presumably due to the relatively small size of these neurones in the goldfish.

7. It would appear that respiratory rhythmicity in the goldfish depends upon mechanism/s not unlike those operating to produce and maintain rhythmic respiration in the cat.

Significance to Mental Health Program:

This is part of a program dealing with the ways in which aggregates of neurones in the brain-stem control autonomic functions.

Proposed Course of Project:

The project, insofar as experimentation with the goldfish is concerned, has been completed. When feasible, further attempts will be made to study basic mechanisms responsible for rhythmic discharges in even lower forms of life.

Part B. Included: Yes [ ] No [x]

PHS-NIH
Individual Project Report
Calendar Year 1960

Serial No. M-NC(S.E.)- BS 14
1. Clinical Neuropharmacology Research Center
2. Section on Behavioral Sciences
3. Saint Elizabeths Hospital

Part A.

Project Title: Identification and Localization of Neurones which Control Cardiovascular Phenomena

Principal Investigator: G. C. Salmoiraghi

Other Investigators: None

Cooperating Units: None

Man Years: (calendar year 1960)

Total:	.48
Professional:	.33
Other:	.15

Patient Days (calendar year 1960)
0

Project Description:

Objectives:
To study the way by which aggregates of neurones in the brain-stem control arterial pressure and other cardiovascular phenomena.

Methods Employed:
Extracellular recording from individual units in the cat's brain-stem. For the purpose of this study, "a cardiovascular neurone" is provisionally defined as "a neurone whose pattern of discharge is modified by activation or deactivation of presso- and chemo- receptors". Experiments are carried out in unanaesthetized, decerebrated, decerebellated, thoracotomized, artificially respired cats.

Material:
Cats

Major Findings:
1. During systematic exploration of the brain-stem from the obex to the inferior colliculi, neurones whose rate of discharge was modified concomitantly with blood pressure changes induced by intravenous injection of from 1 to 3 mcg. of noradrenaline and histamine, or concomitantly with a blood pressure change occurring during Mayer's waves, were found scattered throughout the medulla and in the medial portion of the pons. Over 100 neurones were

Part A.

investigated.

2. One-third of the "cardiovascular neurones" encountered ("population one") increased their rate of discharge simultaneously with a blood pressure rise, either induced by noradrenaline or occurring spontaneously during Mayer's waves. Conversely, their rate of discharge decreased during a fall of blood pressure caused by histamine or during the falling phase of a Mayer's wave.

Two-thirds of the "cardiovascular neurones" encountered ("population two") behaved in the opposite way, i.e., their rate of discharge decreased during a pressor response following intravenous injection of noradrenaline (1 to 3 gammas) or during a rise in blood pressure occurring when Mayer's waves were present. Conversely, their rate of discharge increased during a depressor response caused by intravenous injection of histamine (1 to 3 gammas) or during the falling phase of a Mayer's wave.

3. Occlusion of one common carotid artery in cats in which the other three buffer nerves had been removed decreased or stopped the discharge of "population one" neurones and increased the discharge of "population two" neurones.

Significance to Mental Health Program:

This is part of a program of research dealing with the ways in which aggregates of neurones in the brain-stem control autonomic functions.

Proposed Course of Project:

This is one of a series of investigations which will attempt to clarify: (a) the localization and patterns of discharge of "cardiovascular neurones"; (b) the types of neurones participating in the control of cardiovascular phenomena; (c) the mechanism/s responsible for the repetitive discharge of such neurones; (d) the site and mode/s of action of afferent impulses from presso- and chemo- receptors; (e) the site and mode of action of CO_2; and (f) the nature of hypothetical neurohumoral agents operating to produce excitation and inhibition of these neurones.

Part B Included: Yes [ ] No [x]

PHS-NIH
Individual Project Report
Calendar Year 1960

Serial No. M-NC(S.E.)- BS 15
1. Clinical Neuropharmacology Research Center
2. Section on Behavioral Sciences
3. Saint Elizabeths Hospital

Part A.

Project Title: Studies of Sexual Behavior

Principal Investigator: Richard E. Whalen

Other Investigators: Lewis Thaxton and Norris G. Mann, Jr.

Cooperating Units: None

Man Years: (calendar year 1960)

Total:	1.5
Professional:	1.0
Other:	0.5

Patient Days (calendar year 1960)
0

Project Description:

Objectives:
These studies represent an attempt to describe and understand the environmental and physiological dynamics of a relatively simple and stable behavior pattern. The psychological studies are designed to isolate the effects of prolonged mating (e.g., effects of intromission and ejaculation), and the stimulus factors which induce mating and cause the cessation of mating. The physiological studies are designed to delimit the areas of the central nervous system which are concerned with sexual arousal, ejaculation, and the effects of prolonged mating.

Methods Employed:
Male cats and rats are allowed to mate for extended periods; their sexual behavior is observed and recorded. Stimulus factors are varied by the selective use of female partners and the time since the previous mating session.

The physiological methods now in use center upon standard electrical stimulation of the peripheral nerves of the penis with concurrent recording of evoked potentials in the central nervous system.

Major Findings:
Since the experiments have not yet been completed, no summary of major findings can be given.

Part A.

Significance to Mental Health Program:

The complete analysis of a unitary behavior pattern, such as sexual behavior, can contribute to the understanding of the precise stimulus-response integrations involved in normal behavior, or its disruption.

Proposed Course of Project:

Future research will deal with electrical recording from chronic electrodes in the central nervous system during mating. Alterations in the patterns of electrical activity and behavior will be produced by behavioral and pharmacological manipulations in order to further the analysis of the relations between the nervous system and behavior.

Part B Included: Yes [ ] No [x]

PHS-NIH
Individual Project Report
Calendar Year 1960

Serial No. M-NC(S.E.)- BS 16
1. Clinical Neuropharmacology Research Center
2. Section on Behavioral Sciences
3. Saint Elizabeths Hospital

Part A.

Project Title: Analysis of Potentials Evoked by Sound in the Auditory Cortex of the Intact Unanesthetized Cat

Principal Investigators: Robert J. Gumnit and Robert G. Grossman (WRAIR)

Other Investigators: None

Cooperating Units: Department of Neurophysiology
Walter Reed Army Institute of Research

Man Years: (calendar year 1960)		Patient Days (calendar year 1960)
Total:	.70	0
Professional:	.35	
Other:	.35	

Project Description:

Objectives:
To develop a method of recording Direct Current activity from the cortex of intact, unanesthetized cats and to subject such activity to physiological analysis.

Methods Employed:
A very sensitive Direct Current recording system using chronically implanted non-polarizable electrodes and either an ink-writing oscillograph or a cathode-ray oscilloscope was employed to record from the cortex of unanesthetized intact cats.

Material:
Cats

Major Findings:
A method of chronically implanted non-polarizable calomel electrodes in cats was developed.

Direct Current potential changes in response to auditory stimulation, previously investigated only in anesthetized animals, were found in the unanesthetized cats. In addition, certain components of the click evoked potentials were found to be of longer duration than previously thought and to undergo alterations with changes in background auditory activity.

Part A.

Significance to Mental Health Program:

A method was developed which permits recording from unanesthetized cats electrical activity of the brain heretofore analyzed only in anesthetized preparations. This activity may possibly be related to behavioral changes in the normal animal as well as to the handling of sensory information by the brain. It is believed that this investigation deals with an area of basic brain physiology.

Proposed Course of Project:

Terminated. A paper dealing with this material is being prepared for publication.

Part B Included: Yes [x] No [ ]

Part B.

Honors, Awards and Publications:

Paper presented at the American EEG Society meeting in Boston, June, 1960: Gumnit, Robert J., and Grossman, Robert G.: Evoked Slow Wave Phenomena in Auditory Cortex of Unanesthetized Cat.

PHS-NIH
Individual Project Report
Calendar Year 1960

Serial No. M-NC(S.E.)- BS 17
1. Clinical Neuropharmacology Research Center
2. Section on Behavioral Sciences
3. Saint Elizabeths Hospital

Part A.

Project Title: Development of a Mechanical Microinjector.

Principal Investigator: Arthur S. Schwartz

Other Investigators: Norris G. Mann, Jr.

Cooperating Units: NIH Instrument Fabrication Section

Man Years: (calendar year 1960)

Total:	.35
Professional:	.05
Other:	.30

Patient Days: (calendar year 1960)

None

Project Description:

Objectives:

This project has attempted to develop a combination microinjector and microelectrode which will allow recording from a single unit and simultaneous injection of about 100 cubic microns of a liquid within the vicinity of the cell.

Methods Employed:

A concentric micropipette, consisting of an outer glass delivery tube and an inner glass microelectrode, seated in a drug chamber, has been designed and partially tested. This instrument, together with an attached eccentric cam for ejection, was constructed by the NIH Instrument Fabrication Section. An inert substance placed into the tip of the drug pipette prevents diffusion of the preloaded agent. The eccentric cam allows delivery of extremely small volumes of fluid by mechanical means.

Material:

10 cats

Major Findings:

In a large proportion of our experiments, recording from the same single unit became impossible after ejection of the holding plug. In those cases where the cell's activity continued to be observed after ejection and subsequent drug delivery, a change in firing rate was observed.

Part A.

Significance to Mental Health Program:

Development of a simple mechanical microinjector should facilitate more neuropharmacological and neurophysiological research on a cellular level.

Proposed Course of Project:

We suspect that ejection of the plug often results in losing our cell. An attempt will be made to remove this objection by increasing the distance between recording tip and drug pipette, thus decreasing the likelihood that the inert plug will affect the cell.

Part B. Included: Yes [ ] No [x]

PHS-NIH
Individual Project Report
Calendar Year 1960

Serial No. M-NC(S.E.)-BS 18
1. Clinical Neuropharmacology Research Center
2. Section on Behavioral Sciences
3. Saint Elizabeths Hospital

Part A.

Project Title: Correlation of the Effect of Psychotomimetic Agents on Evoked Potentials and Behavior

Principal Investigator: Arthur S. Schwartz

Other Investigators: Bonnie J. Peacock and Norris G. Mann, Jr.

Cooperating Units: None

Man Years: (calendar year 1960)

Total:	.80
Professional:	.30
Other:	.50

Patient Days (calendar year 1960)
0

Project Description:

Objectives:
Previous studies have shown that small doses of LSD enhance cortical visual and auditory evoked potentials, and enhance evoked potentials of the lateral geniculate body. Larger doses depress potentials in the lateral geniculate. Evarts studied the effects of LSD on the behavior of monkeys, and found that large doses resulted in loss of visual responsivity with simultaneous retention of auditory responsivity. This was also found in other experiments. The present project proposes to study simultaneously the effects of various psychotomimetic agents on visual and auditory responses, recorded both electrophysiologically and behaviorally.

Methods Employed:
Acute anesthetized and decerebrated cats have been studied, recording evoked potentials from the visual system (lateral geniculate and visual cortex) and the auditory system (cochlear nucleus and auditory cortex) simultaneously. Varying doses of LSD and bufotenin have been injected via the intravenous, intracarotid and intraperitoneal routes. The effects of route and dosage were examined on the amplitude of evoked potentials in response to light flashes and clicks.

Material:
Cats

Part A.

Major Findings:

The cochlear nucleus remains somewhat resistant to the influence of LSD, irrespective of route of administration and range of doses. The lateral geniculate is much more sensitive, showing a slight depression with intravenous injections and a more marked enhancement with intracarotid injections. Cortical evoked potentials were too variable to characterize any consistent effects.

Significance to Mental Health Program:

A possible demonstration of localized neuropharmacological effects of psychotomimetic agents, correlated with behavioral effects, may lead to more insight into the mode of action of these agents.

Proposed Course of Project:

Chronically implanted, unanesthetized cats will be studied both behaviorally and electrophysiologically. Simultaneous recordings of evoked potentials in the cochlear nucleus, lateral geniculate body, and auditory and visual cortices will be studied, together with the responsivity of the animal to the relevant stimuli.

Part B Included: Yes [ ] No [x]

PHS-NIH
Individual Project Report
Calendar Year 1960

Serial No. M-NC(S.E.)-BS 19
1. Clinical Neuropharmacology Research Center
2. Section on Behavioral Sciences
3. Saint Elizabeths Hospital

Part A.

Project Title: Role of the Visual Cortex in Flicker Discrimination and the Critical Flicker Frequency (CFF) in the Cat.

Principal Investigator: Arthur S. Schwartz

Other Investigators: Norris G. Mann, Jr.

Cooperating Units: None

Man Years: (calendar year 1960)

Total:	.95
Professional:	.65
Other:	.30

Patient Days (calendar year 1960)
0

Project Description:

Objectives:

The cortex has been implicated as the limiting mechanism in perceiving increasing rates of flicker. Lindsley has suggested that the observed correlation between CFF and the cortical photic following limit implicates the latter structure as the determining mechanism in CFF. Previous work by the present investigator has shown that in chronically implanted cats the cortex may photically follow at frequencies from 10 to 18 cycles per second higher than the behavioral CFF. To further determine whether the cortex is involved, the visual cortex will be ablated and the effect noted on flicker discrimination and the CFF of cats.

Methods Employed:

Suitable apparatus has been constructed. Cats will be trained to discriminate between a flickering and a steady light. After learning, the flicker rate will be increased until no discrimination is evident, and the flicker-fusion threshold then identified. The visual cortex will then be removed by suction and the animals retested for flicker discrimination, and the CFF again determined.

Material:

Cats

Part A.

Major Findings:

Five cats have started training, and three of these have progressed to the point of discriminating between a steady light and a low rate of flicker.

Significance to Mental Health Research:

The above study may contribute to knowledge as to the way in which sensory information is coded by the nervous system.

Proposed Course of the Project:

The CFF's of the first group of animals has yet to be determined. If ablation of the visual cortex does not result in loss of flicker discrimination ability, or does not alter the CFF, another group of animals will be implanted and recordings taken from various sites in order to observe the course of the trace conditioned stimulus (photic following) during flicker discrimination and at the flicker-fusion threshold.

Part B. Included: Yes [ ] No [x]

PHS-NIH
Individual Project Report
Calendar Year 1960

Serial No. M-NC(S.E.)-BS 20
1. Clinical Neuropharmacology Research Center
2. Section on Behavioral Science
3. Saint Elizabeths Hospital

Part A.

Project Title: Generalization gradients for reward-controlled and punishment-controlled behavior

Principal Investigator: Eliot Hearst

Other Investigators: None

Cooperating Units: None

Man Years: (Calendar year 1960)
Total: .25
Professional: .25
Other: 0

Patient Days (calendar year 1960)
None

Project Description:

Objectives:
The extent to which subjects will respond to a stimulus which is not exactly the stimulus to which they were originally conditioned, i. e. the extent to which the conditioned stimulus "generalizes", may be a function of the type of motivation controlling the behavior being measured. Study is being made of visual intensity generalization gradients under conditions of either reward or punishment.

Methods Employed:
Rhesus monkeys were first trained in the presence of a bright light to depress a lever to prevent shocks and to pull a chain to receive food pellets. Subjects were then tested with a variety of lights, all dimmer than the conditioning stimulus, and the frequency of lever-pressing and chain-pulling to each intensity was recorded.

Material:
5 young Rhesus monkeys, who learned to lever-press and chain-pull in a Foringer Carnivore Cage with accessory operant-conditioning equipment.

Part A.

Major Findings:

(1) Generalization gradients for punishment-controlled behavior were much flatter than for reward-controlled behavior; much more stimulus generalization occurs under aversive conditions than under reward conditions.

(2) After discrimination training (i.e. when animals are specifically trained to respond to a bright light and not to respond to a dim light, or vice-versa), both gradients are much steeper, but avoidance gradients are still flatter than reward gradients.

Significance to Mental Health Program:

It has been noted previously that amount of stimulus generalization differs for schizophrenics and "anxious" subjects, as opposed to normals. The experimental study of stimulus generalization, especially as related to motivation, may provide clues as to why these differences occur.

Proposed Course of Project:

Other monkeys are being studied in auditory conditioning experiments, to see if the same findings hold true for other than visual cues. The effects of drugs on generalization is a little-investigated problem, which will be studied. There is prior evidence that certain parts of the brain (e.g. amygdala) have specific functions with regard to stimulus generalization and discrimination and it is planned to examine this aspect further.

Part B. Included: Yes [x] No [ ]

Part B.

Honors, Awards, and Publications

Publication: Hearst, E. Visual generalization gradients obtained simultaneously for reward-controlled and punishment-controlled behavior. Science, 1960 (in press).

PHS-NIH
Individual Project Report
Calendar Year 1960

Serial No. M-NC(S.E.)- BS 21
1. Clinical Neuropharmacology Research Center
2. Section on Behavioral Science
3. Saint Elizabeths Hospital

Part A.

Project Title: "Resistance to extinction" functions in the single organism

Principal Investigator: Eliot Hearst

Other Investigators: None

Cooperating Units: None

Man Years: (calendar year 1960)
Total: .25
Professional: .25
Other: 0

Patient Days (calendar year 1960)
None

Project Description:

Objectives:
Most of the behavioral functions which relate response strength (as measured by "resistance to extinction") to certain independent variables have been obtained in group experiments. Our objectives were (1) to determine the feasibility of a technique for obtaining such relationships in single subjects and (2) to compare these relationships with those obtained in classical group experiments.

Methods Employed:
Pigeons were initially trained to peck a disc which could be illuminated with 4 possible colors. Under each color a different value of some independent variable was in effect, e.g., number of reinforcements in one experiment, number of responses required for reinforcement in another experiment. The responses were then extinguished in a situation where all 4 colors were presented equally often, and response strength to each stimulus was recorded.

Material:
12 white Carneaux pigeons, trained to key-peck in a standard operant-conditioning situation.

Part A.

Major Findings:

(1) The technique proved practical, as both individual animals and the grouped data for the total subjects showed consistent relationships as a function of changes in the indepenedent variable.

(2) "Resistance to extinction" increased as a function of number of reinforcements in one experiment, and as a function of number of responses required for reinforcement in another experiment. Individual functions, though fairly consistent from bird to bird, showed more variability than data grouped together for all subjects.

Significance to Mental Health Program:

The laws of learning, and variables affecting learning, have pertinence to the acquisition and maintenance of abnormal behavior, as well as normal behavior. The present method may be a more efficient and productive way of examining many topics in the field of learning.

Proposed Course of Project:

No further work on this technique is planned for the immediate future.

Part B Included: Yes [x] No [ ]

Part B.

Honors, Awards, and Publications

Publication: Hearst, E. "Resistance to extinction" functions in the single organism. J. exper. Analysis of Behavior, 1961 (in press).

PHS-NIH
Individual Project Report
Calendar Year 1960

Serial No. M-NC(S.E.)-BS 22
1. Clinical Neuropharmacology Research Center
2. Section on Behavioral Sciences
3. Saint Elizabeths Hospital

Part A.

Project Title: Delayed-Alternation responding in the pigeon, and the effects of drugs on this behavior.

Principal Investigator: Eliot Hearst

Other Investigators: Yvonne Leacock, and Arthur Kales

Cooperating Units: None

Man Years: (calendar year 1960)

Total:	1.25
Professional:	.25
Other:	1.00

Patient Days: (calendar year 1960)

None

Project Description:

Objectives:

Situations in which animals are forced to delay the execution of a correct response for several seconds or minutes are often considered to be more analogous to "intellectual" functioning in humans than are other "simpler" aspects of animal behavior. In addition, such behavior has been shown in monkeys to be greatly impaired by lesions in certain parts of the brain (e.g. frontal lobe) which are thought important in "memory" and the "higher mental processes" in humans. The objective of the present study was two-fold: (1) to determine accuracy of a delayed response in the pigeon as a function of delay interval (from 1 to 10 seconds) and (2) to examine the effects of various drugs - scopolamine, amphetamine and pentobarbital-on this sort of performance.

Methods Employed:

Pigeons were initially trained to peck at two keys in order to obtain grain reinforcement. Then the delayed-alternation procedure was begun, in which rewards were given only for a response to the key which was not rewarded on the immediately preceding trial; in this procedure birds had to "remember" which key had been correct on the preceding trial in order to make a "correct" response. Consistent alternation of key-pecks on the two keys was ideal performance. The inter-trial interval (during which all lights in the cage were turned out) was varied between 1 and 10 seconds in each subject.

Part A.

Material:

8 white Carneaux pigeons, which responded in a standard operant-conditioning situation.

Major Findings:

(1) Birds exhibit at least 80% accuracy on inter-trial delays of from 1 up to 5 seconds, but are only about 65-70% accurate on longer delays of 10 seconds. Observation of the subjects revealed that they adopted distrust orienting postures as cues for correct responding, i.e. they spent time in inter-trial period stretching their heads in the direction of the next-to-be-correct key, or faced their bodies towards that key, etc.

(2) Scopolamine, amphetamine and pentobarbital in commonly-used doses, all had an adverse effect on delayed-alternation behavior. Subjects were much less accurate and long pauses in responding often occurred under these drugs.

Significance to Mental Health Program:

A study of behavior under complex reinforcement contingencies and its disruption or improvement by drugs may give clues about complex behavioral processes in humans. A situation such as the present one might prove useful as a screening device for new pharmacological compounds which are thought to have effects on "memory" and other higher functions.

Proposed Course of Project:

No further work in this area is contemplated at the present time.

Part B. Included: Yes [ ] No [x]

Serial No. M-S-T(C)-12
1. Socio-environmental Studies
2. Social Studies in Therapeutic Settings
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Attitudes of Nursing Personnel Toward Relationships with Patients in a Mental Hospital

Principal Investigator: Leonard I. Pearlin

Other Investigators: Morris Rosenberg

Cooperating Units: Saint Elizabeths Hospital

Man Years (calendar year 1960):		Patient Days (calendar year 1960):
Total	2 5/6	None
Professional	1	
Other	1 5/6	

Project Description:

Objectives: To identify therapeutically crucial attitudes among nursing personnel; develop methods for their measurement; investigate the social and psychological characteristics of nursing personnel and the structure of the settings in which they work that give rise to these attitudes.

Methods Employed: From a search of the relevant literature and a number of unstructured interviews with nursing personnel and conferences with experts in the field of mental hospital milieu, two fundamental instruments emerged: (1) a self-administered structured questionnaire and (2) a ward information form. The questionnaires were filled out and returned by 1138 nursing personnel or 87 per cent of the total to whom the questionnaires were addressed. This document taps a variety of attitudes toward the occupation, conditions of work and patient care, as well as personal and social characteristics of each of the respondents. The ward information form, addressed to each of the 156 wards of the Hospital, asks for factual information about characteristics of the patient population, ward policies and programs, and staffing patterns. The basic model followed in the

analysis of the data thus far is to examine the interplay between staff characteristics and characteristics of the wards to which they are assigned in the arousal of attitudes.

Major Findings: The analysis of the data has produced findings in four areas: (1) factors that create feelings of psychological distance from patients; (2) the social and psychological factors that regulate faith in the therapeutic efficacy of drugs; (3) group influences on attitude formation among nursing personnel; and (4) the appeals of anonymity in questionnaire administration.

Psychological distance is of two kinds: status distance and personal distance. Status distance is the withdrawal from patients by setting one's self above patients. These are the conditions that lead to status distance: where one has a relatively high position in the nursing service and is assigned to patients of relatively low social standing; where one has an obeisant or honorific regard of his own superiors in the hospital; and finally, where one strongly aspires to occupational mobility in a situation where mobility is closed to him. Personal distance, by which is meant the absence of any positive emotional feelings for patients, tends to be regulated by conditions of role congeniality. There is a tendency for nursing personnel to exhibit least personal distance when working with patients of their own age. However, female personnel working with patients of the opposite sex express less personal distance than in any other combination of the roles of nurse and patient by sex.

The major finding to come out of the analysis of faith in drugs is that the standards for judging the effects of drugs on patients are derived from the effects drug usage has on occupational roles. Thus staff who are primarily interested in patient control and management are highly enthusiastic about the effects of drugs on patients. Personnel more oriented to providing service to patients, however, are less enthusiastic about drug effects.

The attitudes expressed by individuals have been shown to be influenced by the normative opinions of ward groups. The conditions that contribute to this consensus are: frequent interaction among personnel, participation in decision making processes and close positive feelings among ward peers. Under these conditions personnel

assigned to the same ward are likely to share common attitudes and opinions.

The last area in which findings have been made is methodological. Comparing nursing personnel who signed their names to their questionnaires with those who remained anonymous, it was discovered that certain personality characteristics of respondents were more important than the nature of the questions asked. Respondents who have little confidence in themselves, who have a generally distrustful view of others and lack a capacity for involvement in the tasks they must perform are most likely to be attracted to anonymity.

Scientific Significance: Recent work has pointed up the importance of nursing personnel in the milieu of mental patients. In particular, the attitudes they hold toward patients and the communication of these attitudes to patients are critical factors influencing the therapeutic effectiveness of nursing personnel. This study represents an attempt to measure attitudes generally felt to be of significance and to understand the determinants of these attitudes.

At the same time, this study aims to develop a set of techniques and a methodology for obtaining core information that is useful in the evaluation of specific therapeutic programs. For example, the attitudes being dealt with in this study could be applied to an investigation of the effectiveness of the tranquilizing drugs.

Proposed Course of Project: The analysis of the data will continue during the next year. At the same time, much of the material in this study will be included in a ten hospital cooperative study initiated by the Psychopharmacology Service Center. This study entails an evaluation of hospital milieu and will provide an opportunity to extend our analysis to other hospital settings.

Part B included Yes [ ] No [x]

Serial No. M-S-T(C)-13
1. Socio-environmental Studies
2. Social Studies in Therapeutic Settings
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Development of Self-Image and Self-Ideals in Normal Adolescence

Principal Investigator: Morris Rosenberg

Other Investigators: None

Cooperating Units: None

Man Years (calendar year 1960):		Patient Days (calendar year 1960):
Total:	-	None
Professional:	-	
Other:	-	

Project Description:

The principal investigator transferred to Basic Research during the year. For a full description of this project see Section on Community and Population Studies, Basic Research, Serial No. M-S-P-8.

Serial No. M-S-T(C)-16
1. Socio-environmental Studies
2. Social Studies in Therapeutic Settings
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: A Study of Healthy Persons in Adolescence: Resources in Coping with a Transition to a New Environment

Principal Investigator: Earle Silber

Other Investigators: David Hamburg, Morris Rosenberg, George Coelho, Irwin Greenberg, Leonard I. Pearlin, and Elizabeth Murphy

Cooperating Unit: Adult Psychiatry Branch

Man Years (calendar year 1960):		Patient Days (calendar year 1960):
Total:	1/3	
Professional:	1/3	None
Other:	--	

Project Description: Described in full by the Adult Psychiatry Branch, Project Serial No. M-AP(C)-15.

Part B included: Yes [ ] No [x]

Serial No. M-S-T(C)-17
1. Socio-environmental Studies
2. Social Studies in Therapeutic Settings
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: An Exploratory Study of Explanations for Success and Failure of Therapeutic Programs in a Psychiatric Setting

Principal Investigator: Yngvar Löchen

Other Investigators: None

Cooperating Units: Saint Elizabeths Hospital

Man Years (calendar year 1960):		Patient Days (calendar year 1960):
Total:	3/4	
Professional:	1/2	None
Other:	1/4	

Project Description:

Objectives: (1) To examine the perceptions, definitions, and explanations of different types of success and failure in a psychiatric setting among those occupying different organizational positions; (2) to investigate the consequences of differential perceptions for the introduction and effectiveness of new therapeutic programs.

Previous work indicates that some members of the hospital staff will interpret the success or failure of a therapeutic program in terms of the qualities of the individuals involved, whereas others will view it in the light of the organizational structure of the hospital. It is suggested that the likelihood that such changes in the therapeutic milieu will be introduced in the first place, or, if once introduced, will be successful, will depend on the frames of reference held by those occupying positions of authority in the hospital.

The interest originated from an earlier study by the investigator of a Norwegian mental hospital in which the impression emerged that various groups defined and interpreted success or failure in different ways. It is hoped

that by adding data obtained in another mental hospital, in this case an American one, it will be possible as a by-product of this study to develop certain preliminary hypotheses regarding those elements which are inherent to the structure of the formal organization and those which are expressions of cultural variations. Such hypotheses, in turn, may reveal those elements in mental hospital structure which can be manipulated to increase therapeutic effectiveness and those which are resistant to such changes.

Methods Employed: Participant observation and interviewing of staff members at the Dikemark Hospital in Norway and Saint Elizabeths Hospital in Washington, D. C.

Major Findings: Mr. Löchen is now refining his analysis of the data from the Dikemark Hospital and beginning a comparative analysis of the Norwegian and American mental hospitals. There are no conclusive findings as yet.

One major reason for Mr. Löchen's coming to this laboratory was to secure methodological training unavailable to him in Norway. One result of his experience was a paper, now in draft form, codifying the procedures of participant observation in a mental hospital, and considering the advantages and limitations of this procedure as contrasted to more formal methods of inquiry.

Scientific Significance: In recent years data have accumulated suggesting that the hospital milieu may exercise an important influence upon the patient's clinical course of recovery. One major ingredient of this milieu is the degree of integration or agreement which exists among the various levels of the hospital staff. It is hoped that the focus upon the differential interpretations of success and failure may yield insights into those conditions producing conflict and permanent misunderstandings among hospital personnel and those which foster harmony of views.

Proposed Course of Project: Mr. Löchen, who was here for one year as a Visiting Scientist, has returned to his native Norway to complete the analysis begun here and to undertake further research in Norwegian mental hospitals.

Part B included Yes [ ] No [x]

Serial No. M-S-T(C)-18
1. Socio-environmental Studies
2. Social Studies in Therapeutic Settings
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: An Experimental Study of the Affiliative Behavior of Chronic Schizophrenics

Principal Investigator: Carmi Schooler

Other Investigator: None

Cooperating Units: Springfield State Hospital

Man Years (calendar year 1960):		Patient Days (calendar year 1960):
Total:	1	
Professional:	1/2	None
Other:	1/2	

Project Description:

Objectives: This study represents an attempt to investigate experimentally the relationship between the reluctance of the regressed chronic schizophrenic to affiliate with others and such other factors as his present intellectual functioning and his pre-morbid level of social adjustment.

Methods Employed: The subjects were sixty hospitalized regressed chronic schizophrenic women whose level of pre-morbid social adjustment had been rated on the basis of the Phillips scale. The method of measuring affiliative behavior in an experimental setting which has been developed by Schachter was employed in the study. Each subject was brought to the experimental setting and told that the psychologist was not yet ready for her. She was then asked to wait, and was shown a waiting room containing two open alcoves--an empty one and one in which a confederate of the experimenter was sitting, dressed as a patient. The subject was then told that she could wait in either alcove. Her choice of alcove and her reactions to the confederate served as measures of her desire for social affiliation. After four minutes of waiting, the subject was taken to the psychologist who administered the Wechsler Adult Intelligence Scale, a 10-response Rorschach, and a word association test.

Major Findings: The analysis of the data is being completed.

Scientific Significance: The two symptoms most frequently reported as typifying the chronic schizophrenic are the presence of cognitive and perceptual distortion and the decline in the tendency to seek social interaction. The present study seeks to discover whether these two symptoms vary independently or whether a decline in one area necessarily involves a decline in the other. A measure of premorbid social integration has been included in the study to test the existence of a persistent affiliative trait which causes social integration to remain relatively more socially motivated after becoming chronically ill.

Proposed Course of Project: The IBM analysis of the data is being completed. When the analysis is completed the results will be prepared for publication.

Part B included: Yes [x] No [ ]

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B: Honors, Awards, and Publications

Publications other than abstracts from this project:

Schooler, C. and H. Spohn, "The Susceptibility of Chronic Schizophrenics to Social Influence in the Formation of Perceptual Judgments," Journal of Abnormal and Social Psychology, September, 1960.

Honors and Awards relating to this project:

None

Serial No. M-S-T(C)-19
1. Socio-environmental Studies
2. Social Studies in Therapeutic Settings
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Investigation of the Relationship Between Birth Order and Schizophrenia

Principal Investigator: Carmi Schooler

Other Investigators: None

Cooperating Units: Springfield State Hospital

Man Years (calendar year 1960):		Patient Days (calendar year 1960):
Total:	$\frac{1}{2}$	None
Professional:	$\frac{1}{4}$	
Other:	$\frac{1}{4}$	

Project Description:

Objectives: To determine whether ordinal position in a sibling group is related to chronic schizophrenia.

Methods Employed: Review of published and unpublished literature, and collection of birth order and social background data from records of a 25% sample of the schizophrenic female patients in Springfield State Hospital.

Major Findings: (1) In a sample of hospitalized female schizophrenics drawn for this study, significantly more patients come from the last half of their sibling group than from the first half. (2) In a sample of discharged patients there were disproportionately large numbers of last-half catatonics and first-half paranoids. From the data at hand it cannot be concluded whether this finding is true only for discharged patients since a similar though not significant trend exists among the hospitalized population. (3) In general, when the data from various studies are combined, significantly more of the subjects are last-born than first-born. This difference, however, appears to be entirely due to subjects from families of four or more. (4) It is impossible with the data at hand to

separate the effect of birth order and maternal age.

Scientific Significance: The results provide definite evidence of a non-genetic component in the etiology of schizophrenia, and a source of hypotheses about the nature of such non-genetic factors.

Proposed Course of Project: A follow-up is now being planned to evaluate the relative effect of birth order and maternal age on schizophrenia.

Part B included Yes [x] No [ ]

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B: Honors, Awards, and Publications

Publications other than abstracts from this project:

Schooler, Carmi, "Birth Order and Schizophrenia," The American Medical Association Archives of General Psychiatry (accepted for publication).

Honors and Awards relating to this project:

None

Serial No. M-S-T(C)-21
1. Socio-environmental Studies
2. Social Studies in Therapeutic Settings
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Affiliation Among Chronic Schizophrenics: Choice of Partner

Principal Investigator: Carmi Schooler

Other Investigators: None

Cooperating Units: Saint Elizabeths Hospital

Man Years (calendar year 1960):		Patient Days (calendar year 1960):
Total:	3/4	None
Professional:	1/4	
Other:	1/2	

Project Description:

Objectives: To investigate some possible factors in the chronic schizophrenics' attitudes toward social interaction by asking subjects to select the value and behavior patterns they prefer in individuals with whom they are expected to socialize.

Methods Employed: Subjects will be told that we are developing a series of psychological tests which require individuals to work in pairs. They will also be told, "Since we want you to do well in the tests, it is important that you have a partner you think is right for you." The subjects will then be asked a series of questions about the characteristics they would prefer to find in such a partner. After the data are gathered, the subjects will be told that we are not able to continue testing as planned, and will be given a small reward for their cooperation. The planning stage of this study has just been completed.

Major Findings: Pre-testing is presently underway and will have to be finished before a full-scale study can be started.

Scientific Significance: It is hoped that the present study will provide information about those attitudes of the chronic schizophrenic which result in their disruption when they are faced with experimentally induced social contacts and their virtual abstention from voluntary social interaction.

Proposed Course of Project: Pre-test data are now being collected. This must be analyzed before the further course of the project can be fully planned. .

Part B included Yes [x] No [ ]

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B: Honors, Awards, and Publications

Publications other than abstracts from this project:

Schooler, C. and H. Spohn, "Social Interaction on a Ward of Chronic Schizophrenics," International Journal of Social Psychiatry, Vol. 6, Nos. 1 and 2, Summer, 1960, pp. 115-119.

Honors and Awards relating to this project:

None

Serial No. M-S-T(C)-22
1. Socio-environmental Studies
2. Social Studies in Therapeutic Settings
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Comparative Socialization in Selected Primitive, Transitional, and Contemporary Cultures

Principal Investigator: Stanley Diamond

Other Investigators: None

Cooperating Units: None

Man Years (calendar year 1960):		Patient Days (calendar year 1960):
Total:	$\frac{1}{4}$	None
Professional:	$\frac{1}{4}$	
Other:	-	

Project Description:

Objectives: To ready for publication Arab, and perhaps Israeli, and Nigerian materials, in the general area of comparative socialization, within the historical context of the several cultures. Historical factors, relevant to an understanding of the background of each culture and thus to the overt and covert nature and aims of socialization will be explored further.

It is assumed that the Israeli Kibbutz represents a type of modern collectivism, the Arab village represents a hierarchical and patriarchal society in transition to more or less "Western" modes of behavior, and the Anaguta of North-Central Nigeria represent a type of authentically primitive, communally organized isolate. These three levels of organization--contemporary, transitional, and primitive--imply an over-all historical schema under which studies of socialization relative to the specific history and structure of each society can be subsumed.

The objective of this inquiry, then, is to help broaden and develop the comparative-historical approach

to the individual's culturally determined life cycle, in the hope that this may lead to further understanding of the similarities and differences encountered among societies.

Methods Employed: Field work: Israeli Kibbutz and Arab village from August 1951 to March 1953; Anaguta of North-Central Nigeria from August 1958 to August 1959. Specific techniques included participant observation in the three societies, and other standard anthropological methods. Among the latter were structured and unstructured individual and group interviews, case histories, historical documents, textual and linguistic analyses.

Comprehensive questionnaires in the native language, and informal and formal projective tests, helped balance subjective and purely observational approaches. Samples represented as high as 75 per cent of the population (Kibbutz questionnaire), but never fell below 16 per cent (Arab Rorschachs).

Major Findings: Collective, relatively "family-less" rearing, as in the Israeli Kibbutz, is not self-perpetuating since the children do not "identify" with the institution. These "transitional" children are reminiscent of, but not identical with, maternally deprived children in our own society. Intellectual and emotional lives tend to be restricted and/or specialized.

The key to an understanding of Kibbutz structure and function, including the institutionalized separation between the generations, is the historical rebellion against the traditional European Jewish milieu, most specifically, against the orthodox family. The Kibbutz is, so to speak, the Shtetl (the traditional Jewish community) turned inside out.

Arab society, archaic and hierarchical, strongly oriented to the family, yet politically organized, produces a wide range of psychological types and tensions. The classic "oedipal" process is powerfully reinforced by the structure of Arab culture.

The formal subordination of women, and the severe conflicts associated with it, are crucial to an understanding of Arab culture. Thus the economic, sexual, and domestic roles of Arab women, as these have developed historically, must be grasped if the culture at large,

and socialization in particular, is to be placed in a meaningful context.

Nigerian children, of an authentically "primitive," non-literate social origin, are well-mothered and family oriented. A wide spectrum of tensions is discharged through complexly ramifying contacts with real and artificial kin, heightened at certain points in the life cycle by cathartic and creative ritual behavior. The rituals are "cathartic" in that they serve as occasions for open, if culturally molded, expression of ambivalent feelings about constituted authority, tradition, animal and human nature, and nature at large. They are "creative" in the dramatic elaboration of symbols, the acting out of conflicts, the anticipation and elaboration of new roles for individuals, and the renewal of the vitality of the group. Put another way, the primitive rituals are creative in the reduction and cultural use of anxiety arising out of a variety of existential situations, such as puberty, marriage, divorce, death, birth, and sickness of mind and body. These rituals can, therefore, be termed "expressive" as opposed to the "binding," compulsive, or "ritualistic" behavior encountered as neurotic phenomena among individuals in contemporary society. The primitive ritual also differs from contemporary group rituals in that the latter strive toward repression of ambivalence, rather than its expression and consequent cultural use.

Scientific Significance: Further inquiry into disparate types of socialization, particularly those connected with deprivation, on a scale reading roughly from personal to institutional in appropriate cultures, may help us trace the etiology and characteristic course of certain psychiatric disorders and emotional-intellectual deficiencies. At the same time, definitions of mental health and illness, on cross-cultural bases, may be gradually extended from relativistic and clinical contexts to include culturally sanctioned behavior.

Proposed Course of Project: Analysis of 100 Arab Rorschachs, representing both sexes and all age groups, administered in a village of 600 people; the analysis of these records will be correlated with the socio-cultural and historical background of the local group.

Part B included Yes [x] No [ ]

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B: Honors, Awards, and Publications

Publications other than abstracts from this project:

Diamond, S., "Anaguta Cosmography: The Linguistics and Behavioral Implications," Anthropological Linguistics, 1960, 2: 31-38.

Diamond, S., "Plato and the Definition of the Primitive," in Diamond, S. (ed.), Culture in History: Essays in Honor of Paul Radin, New York: Columbia University Press, 1960.

Diamond, S. (ed.), Culture in History: Essays in Honor of Paul Radin, New York: Columbia University Press, 1960.

Diamond, S., Essay Review of African Continuity and Change, edited by Bascom and Herskovits, American Anthropologist (in press).

Since this is the first time this project has been listed, the following publications from preceding years are relevant:

Diamond, S., "Kibbutz and Shtetl: The History of an Idea," Social Problems, 1957, 5: 70-100.

Diamond, S., "The Kibbutz: Utopia in Crisis," Dissent, Spring, 1957, pp. 133-140 and 146-151. (Reprinted in Voices of Dissent, New York: Grove Press, 1958.)

Honors and Awards relating to this project:

None

Serial No. M-S-T(C)-23
1. Socio-environmental Studies
2. Social Studies in Therapeutic Settings
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Cultural and Psychodynamic Factors in the Occurrence and Treatment of Psychiatric Illnesses in Japan

Principal Investigator: William Caudill

Other Investigators: None

Cooperating Units: None

Man Years (calendar year 1960):
Total: 3/4
Professional: 1/2
Other: 1/4

Patient Days (calendar year 1960):
None

Project Description:

Objectives: 1) To identify and describe the types and symptom patterns of psychiatric illnesses in Japan, and to identify and describe the types of treatment used for these illnesses. 2) To determine the relationship of these types of illnesses and types of treatment to patterns of behavior in Japanese culture. 3) To compare the results obtained with similar data from other cultures.

Methods Employed: 1) Using mainly observation and interviewing, studies were made during 1958-59 of the organization and operation of three contrasting small Japanese psychiatric hospitals located in metropolitan Tokyo. In terms of treatment, the first hospital was organic in its emphasis, the second specialized in Morita psychotherapy, and the third utilized psychoanalytically oriented psychotherapy. 2) Information was obtained through use of interviews and documents on the history and present organization of psychiatry in Japan. 3) A schedule calling for psychiatric and sociological information was constructed and completed for the approximately 600 patients who were admitted during 1958 to the three hospitals which were studied, and for the approximately 200 patients who were admitted in 1958 to a large psychiatric hospital run by the city of Tokyo. 4) A questionnaire asking for information on personal background

and nursing career was administered to approximately 200 student nurses at two schools of nursing in Tokyo. 5) A "picture interview," using a series of eight pictures as visual questions, was devised and used with 80 subjects (divided among doctors, nurses, and patients) in the attempt to obtain data on what impulses were allowable or needed restraint in various life situations. 6) During an earlier year of work, 1954-55, a value orientations schedule was completed for two samples of subjects (one of 422 persons, the other of 619 persons), each sample being equally divided between two generations, and also equally divided between residence in a village, a small city, and an area of metropolitan Tokyo.

Major Findings: Specific findings are not yet available as analyses of the several parts of the data are still in progress. Preliminary and partial results do indicate the following: 1) Compared with the United States, Japan has fewer psychiatric hospitals (and number of beds) relative to population; the average hospital is small (100-200 beds); and the ownership is predominately in private hands. 2) Physical and chemical types of treatment are preferred over various modes of psychotherapy, and these latter are not well-developed as distinct forms of treatment. 3) An unique (though at present changing) pattern of nursing care in private psychiatric hospitals exists in the role of the tsukisoi--these are women who serve the patient as his individual practical nurse and companion on a twenty-four hour a day basis throughout the patient's course of treatment in the hospital. 4) The relation between doctor and patient (relatively independent of the choice of treatment) entails a pattern of emotional expectations by both parties which is in the direction of a "greater personal involvement" than is true of this relation in the United States. The phrase "greater personal involvement" needs, of course, clear definition and refinement, but it is mentioned here as a preliminary finding because a further analysis of this relation is likely to provide a key for understanding some of the differences in the patterning of impulse control and ego defenses in Japanese patients when compared with American patients. 5) Impulses relating to passivity and dependency are very ego-syntonic as they appear in behavior in many areas of Japanese life. This implies that there may be a somewhat different balance between aggressive and erotic drives as these are manifested in the behavior of Japanese patients who are given the same diagnostic labels as patients with grossly similar symptoms in the United States. 6) An analysis of the value orientations data indicates a significant favoring of collateral ways of relating to others (over lineal or individualistic ways of

relating). A more refined analysis of the data by generation and area of residence (village, small city, or metropolis) also indicates that it might be presumed that such relational values are in the process of changing.

Scientific Significance: This study should help to determine the extent and nature of cultural influences on types of psychiatric illnesses and their treatment. On a descriptive level this involves identification of patterns of symptoms and preferred modes of care that are characteristic for a particular culture. On a more conceptual level this study should provide information on the effect of different cultural settings on the development of character structure and ego defenses. The study should also be of use in furthering understanding of the interplay between the human organism and its "average expectable environment" as this concept has been developed by Hartmann and carried further by Erikson. The reasoning in this regard is that both the patterning of the defensive structure of the personality and the nature of the "average expectable environment" are subject to cultural influences throughout the varying stages (or transitional crises) of the life cycle.

Proposed Course of Project: The analysis of data will continue throughout the coming year. It is planned to work with the various materials in the following order: 1) the value orientations schedules, 2) the picture interviews, 3) the questionnaires from student nurses, 4) the schedules from patients at four hospitals (in terms of diagnosis, symptom patterns, sex, sibling rank, and social class), and 5) comparisons of the three hospitals as to their organization and treatment program.

Part B included: Yes [x] No [ ]

PHS-NIH
Individual Project Report
Calendar Year 1960

Part B: Honors, Awards, and Publications

Publications other than abstracts from this project (in 1960):

Caudill, W., "Transnational Communication: The Experiences of an Anthropologist in Japan," presented on April 9, 1960 at a symposium organized by the Committee on International Affairs, Group for the Advancement of Psychiatry (accepted for publication by the Committee on International Affairs).

Caudill, W., Discussion of a paper by Jurgen Ruesch entitled, "The Contributions of Behavioral Scientists to Psychosomatic Medicine," Psychosomatic Medicine (in press).

Since this is the first time this project has been listed, the following publications from preceding years are relevant:

Babcock, C. and W. Caudill, "Personal and Cultural Factors in Treating a Nisei Man," in Seward, G. (ed.), Clinical Studies in Culture Conflict, New York: Ronald Press, 1958.

Caudill, W., "Observations on the Cultural Context of Japanese Psychiatry," in Opler, M. (ed.), Culture and Mental Health, New York: MacMillan, 1959.

Caudill, W., "The Relationship of Anthropology to Psychiatry in the Study of Culture and Personality," Japanese Journal of Psychoanalysis, Vol. 6, No. 3, June, 1959.

Caudill, W., "Similarities and Differences in Psychiatric Illness and Its Treatment in the United States and Japan," Seishin Eisei (Mental Hygiene), published by Nagoya University, September, 1959.

Honors and Awards relating to this project:

None

Serial No. M - AP(c) - 6
1. Adult Psychiatry Branch
2. Section on Family Studies
3. Bethesda, Maryland

PHS - NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Family Relations in Schizophrenia

Principal Investigator: Lyman C. Wynne

Other Investigators: Psychiatrists: Juliana Day; Leslie Schaffer and Dr. Peter Rosenbaum (part year); Thomas Lewis and Carl Wolff (part-time). Psychologists: George Usdansky and Margaret Thaler Singer (consultant). Art Therapist: Hanna Y. Kwiatkowska. Psychiatric Social Workers: Stanley I. Hirsch, Charlotte Wilkie (part year). Research Assistant: Margaret Toohey. Psychiatric Consultants: Irving Ryckoff, Leslie Schaffer, Alexander Halperin, Leslie Farber and Harold Searles.

Cooperating Units:
M-AP: (c) - 16: College Ward Research Group; Nursing and Occupational Therapy Personnel on Nursing Unit 3-West.

Man Years (Calendar Year 1960)		Patient Days (Calendar Year 1960)
Total:	7.25	1851
Professional:	5.25	
Other:	2.0	

Project Description:

Objectives: The overall goal of this project is to examine the family setting in relation to mental disorder, particularly schizophrenic illness. This comprehensive goal can be subdivided into the following major problems:

(1) The detailed, naturalistic description of the characteristics of the familial environment in schizophrenia and varieties of schizophrenia, in comparison with the [illegible] other psychiatric disorders.

(2) Systematic comparison studies in terms of specific family-related hypotheses:

a. A comparison of families having schizophrenic versus nonschizophrenic but psychiatrically ill offspring.

b. A comparison of siblings, schizophrenic versus nonschizophrenic, within the same family.

(3) Construction of a comprehensive theory of psychological development within the family setting to serve as a basis for the interpretation of the descriptive and systematic findings and to aid in the orientation of future research on familial factors in personality growth and the genesis of schizophrenic illness.

(4) The development of the theory and technique of family therapy.

Methods Employed:

Selection of Families: Families are chosen for study in the program with criteria for selection which minimize all presenting differences between families except one: The presence of a schizophrenic versus a nonschizophrenic (but psychiatrically ill and hospitalized) young adult or late adolescent offspring. Each family consists of two biological parents, the hospitalized offspring, and at least one offspring who is not overtly disturbed psychiatrically. Effort is made to match families in terms of social class, class-related values, and capacity to engage in conjoint exploratory psychotherapy.

Methods of Data Collection:

(1) Family Therapy: Those family members who constitute the current operational family meet together in exploratory psychotherapy with one or two therapists. All sessions are tape recorded and most are observed through one-way observation windows.

(2) Individual psychotherapy in selected instances, with several diagnostic and history-taking interviews with each family member.

(3) Art Therapy: With each family during the initial evaluation period, at least two family sessions are held using art therapy techniques for studying [illegible] with extension of family art therapy [illegible] therapy in selected cases.

(4) Home visits: Naturalistic observations in the home with the entire family present is a routine part of the program; staff members having various roles -- psychiatrist, social worker or nurse -- make these visits for periods ranging from several hours to two days.

(5) Nursing observations: Both traditional observations of each individual patient and also the observation of patients interacting with their families, who are encouraged to visit on the nursing unit.

(6) Psychological Testing: Each family member is tested with the Rorschach test, Thematic Apperception tests, Draw-A-Person test, Sentence Completion test and the Minnesota Multiphasic Personality Inventory.

Methods of Research Analysis:

All the material described is available for the naturalistic descriptive accounts of the [illegible] settings and interaction. The psychological tests and the tape recordings of the family therapy sessions have been particularly used in the systematic comparison studies which are underway.

In order to correlate various aspects of family patterns with the degree of schizophrenic illness in the offspring, it has been necessary to rank-order the psychiatrically disturbed offspring along a dimension of degree of schizophrenic illness or tendency. During the past year a variety of ways of specifying the dimension of "schizophreniceness" were empirically tried. A modified paired-comparisons method was used to make consistent rank-order ratings of all the patients seen in the program thus far. Dr. Margaret Thaler Singer, consultant to the project, similarly ranked the of the patients whose psychological tests she had seen. The [illegible]cal ranking and her ranking on the basis of the psychological tests proved to be almost identical. Thus, a satisfactory rank-ordering of the presenting patients is now available for use in the comparison studies of the families.

Dr. Singer has been moving forward brilliantly with a major variety of comparison studies in this program. Given the psychological test protocols of the family members except for the sibs of the presenting patients, Dr. Singer has been able to make remarkably accurate predictions of the schizophrenic or non-schizophrenic characteristics of the patient family members. By looking at the tests of the patient family members, she has attempted to match patient a[illegible] families in a set.

She has now carried out this procedure with 22 families from the Family Studies program. In addition she has matched 11 schizophrenic patients and families tested by the Yale Family studies program headed by Dr. Theodore Lidz, and still more recently has differentiated 20 schizophrenic and 20 neurotic children "blind" from the projective tests of their parents. Focusing particularly upon the form or style of thinking used within the families, Dr. Singer has been trying to specify the criteria with which she has been able to make her predictions and matchings.

A second variety of systematic studies which is underway involves the use of excerpts from the tape recordings of family therapy sessions. Several pilot studies have been conducted in which these excerpts are rated along dimensions which are relevant to the question of the connection between family relationship patterns and degree of schizophrenic illness in offspring. Excerpts from the family therapy with 14 families, seven having a schizophrenic and seven a nonschizophrenic psychiatrically ill offspring, have been selected for the comparison studies currently being conducted. Thus far, excerpts have been selected in which the parents respond to a comment of a therapist and in which there is no indication of the diagnostic characteristics of the offspring. The preliminary results are encouraging with respect to the capacity of the excerpt technique to differentiate successfully the families of schizophrenics and of nonschizophrenics.

A complex investigation being conducted by Mr. George Usdansky using this approach has yielded suggestive results in a pilot study and is now being verified by ratings of the family therapy excerpts made by two outside judges. In this particular study the families have been compared in terms of frequency of occurrence of certain kinds of interpersonal maneuvers which our previous hypotheses indicate may be particularly relevant. Using the rank-order ratings of degree of schizophrenic illness or tendency, it will be possible to compare these independent ratings of the maneuvers used by the parents with the degree of illness of the offspring.

Patient Material	Totals in this Project	
	During 1960	Through 1960
Number of families	10	33
Number of primary patients	10	36
Schizophrenics	(6)	(22)
Nonschizophrenics	(4)	(14)
Number of parents (outpatients)	20	57
Number of siblings	[illegible]	[illegible]
Number of other family members	[illegible]	[illegible]

Major Findings:

During mid-1960 the primary emphasis of this project shifted from the clinical exploration of family patterns to begin a more comprehensive review and description of the available material and a systematic evaluation of certain hypotheses in the light of this data. There will be no attempt here to anticipate the statement of specific findings and conclusions that are emerging, but in a general way it can be stated that differentation of schizophrenic and non-schizophrenic families, and of schizophrenic and nonschizophrenic siblings, is possible in terms of both the psychological test material and the family therapy excerpt studies. Thus far, there has been a striking congruence in the underlying formulations and concepts which are successfully applicable to differentations made with these dissimilar kinds of data.

Significance to the Program of the Institute:

Severely disturbed family relations have been consistently found in the background of schizophrenic patients. This important lead is being followed up in this project in terms of four major unsettled problems:

(1) The details of the characteristics of the familial disturbance;

(2) The specificity, or lack of it, of the familial disturbance in schizophrenia, compared to other varieties of family problems;

(3) The question of whether the familial disturbance is etiological, accentuating, perpetuating, or secondarily reactive to the schizophrenic pathology of the individual;

(4) The detailed mechanisms or means by which familial experience may affect individual schizophrenic illness. The conceptual problems involved in this question have implications and applications for a central problem of mental health and illness - the relation of individual personality development to the social context, especially the family.

The thought disorder in schizophrenia, to which especial attention is being directed in this project currently, [illegible] long been looked upon as a basic feature of the illness, but it [illegible] psychodynamically-oriented workers or has [illegible] as a fixed, or as an "organic", structurally de[illegible] Thus, the impression developed in this project [illegible] order is dynamically functional and is learned through [illegible]

experience of specifiable kind, challenges directly a major objection to environmental theories of the etiology of schizophrenia.

Although this project is primarily oriented toward untangling the relation of family patterns and schizophrenia, the use of family therapy as an exploratory research tool has led to a significant by-product; a contribution to the development of the theory and technique of family therapy, an approach which has recently been achieving considerable recognition as a potentially valuable addition to the therapeutic repertory of psychiatrists.

Proposed Course of Project:

During the coming year it is planned that the major focus will be on writing and research evaluation of the material which has accumulated, with a reduced clinical case load of families being seen. However, to add, at least slowly to the number of families studied and to keep the writing and research evaluation invigorated with currently "live" family observations, a small number of families will continue to be seen clinically and certain other families will be observed and treated jointly with members of the College Ward Research Group. It is planned that during the coming months that major attention will be given to pushing forward with the comparison studies, both conducting new pilot studies and verifying those positive findings which are coming out of the pilot studies. The use of independent judges will be particularly valuable and necessary in these verification studies.

An intensive effort will be made to relate the specific hypotheses and substantive findings to an overall theory of personality development in the family setting. Heightened conceptual attention will also be given to specifying how the diverse varieties of schizophrenic illness relate to diverse family patterns.

Part B Included: Yes.

Part B.. Honors, Awards and Publications

Publications other than abstracts from this project:

Schaffer, L.; Wynne, L. C.; Day, J. and Halperin, A. - "On the Nature and Sources of the Psychiatrist's Experience with the Family of the Schizophrenic" - in press Psychiatry.

Wynne, L. C.; - "Intrafamilial Alignments and Splits, Their Study in Exploratory Family Therapy", in press in Family Dynamics, Family Change, and Family Psychotherapy.

Wynne, L. C.; Ryckoff, I.M.; Day, J. and Hirsch, S. I.; "Pseudo-Mutuality in the Family Relation of Schizophrenics"; reprinted in Modern Introduction to the Family ed. by Norman Bell and Ezra Vogel, Glencoe, Ill. Free Press 1960.

Kwiatkowska, H. Y., "Family Art Therapy" in press in Family Process.

Serial No. M-AP(C) - 9
1. Adult Psychiatry Branch
2. Family Studies Section
3. Bethesda, Maryland

PHS - NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Social Mobility and the Milieu of the Psychiatric Hospital

Principal Investigator: Leslie Schaffer, M.D.

Other Investigators: Leila Deasy, Ph.D. (presently at Catholic University)

Cooperating Units: Laboratory of Socio-Environmental Studies

Man Years (calendar year 1960) Patient Days (calendar year 1960)

Total	0
Professional	0

Project Description:

This project has been terminated since the principal investigator is no longer a member of the staff.

Part B. Included No.

Serial No. M-AP(C)-13

1. Adult Psychiatry Branch
2. Section on Psychosomatic Medicine
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: The Use of Films in the Study of Emotional Responses and Adrenocortical Function

Principal Investigator: David A. Hamburg, M.D.

Other Investigators: Jacob Fishman, M.D., John Mason, M.D., Edward Sachar, M.D., Joseph Handlon, Ph.D.

Cooperating Units: Walter Reed Army Institute of Research, Department of Neuroendocrine Research and Laboratory of Psychology, NIMH.

Man Years (calendar year 1960):		Patient Days (calendar year 1960):
Total:	.6	
Professional	.5	25
Other:	.1	

Project Description:

This project has been incorporated into M-AP(C)-19, Relation of Emotional Behavior and Endocrine Function.

Serial No. M-AP(C)-14

1. Adult Psychiatry Branch
2. Section on Psychosomatic Medicine
3. Bethesda, Maryland

PHS -NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Physiologic Processes in Depressed Patients

Principal Investigator: Ralph Wadeson, M.D.

Other Investigators: John Mason, M.D., Sidney Marvin, M.D., David A. Hamburg, M.D., Joseph Handlon, Ph.D.

Cooperating Units: Walter Reed Army Hospital, Neuropsychiatric Section; Walter Reed Army Institute of Research, Department of Neuroendocrine Research; Laboratory of Psychology, NIMH

Man Years: (calendar year 1960) Patient Days (calendar year 1960)

Total:	1.5
Professional:	.9
Other:	.6

Project Description:

Objectives:

To study the physiology of depressed patients before, during and after electroshock and other therapies.

Methods Employed:

Depressed subjects are to be rated as to degree of distress, depression, agitation, retardation and expression of affect. Blood samples for 17-hydroxycorticosterone are to be drawn at 6:00, 8:00, 10:00 A.M. and 8:00 P.M. to study the diurnal variation of this substance. Also urinary ketosteroid excretion will be measured from three successive eight-hour periods. Autonomic functions will be evaluated by measuring patients' cardiovascular responses to interaction with an examiner. Psychological testing and evaluation will supplement clinical impressions.

Major Findings:

Blood and urine levels of hydrocortisone seem to be elevated in direct proportionality to the severity of the depression with severely retarded patients having levels comparable to those of Cushing's syndrome. Hydrocortisone levels following treatment with electroshock are not yet available for study. Evaluation of cardiovascular autonomic response to interaction with an examiner seems to indicate a less sustained response occurs before treatment.

Significance to Mental Health:

This study is designed to further information concerning the relationship of emotional problems to physical illness.

Proposed Course of Project:

Diurnal variations of 17-hydroxycorticosterone have been studied in depressed patients and data for post therapy evaluation is still pending. Also, data from cardiovascular studies made concomitantly during the course of the depressive illnesses are being analyzed currently.

Part B included No

Serial No. M-AP(C)-15
1. Adult Psychiatry Branch
2. Section on Personality Development
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A:

Project Title: A Study of Healthy Persons in Adolescence: Resources in Coping with a Transition to a New Environment.

Principal Investigator: Earle Silber, M. D.

Other Investigators: David Hamburg, M. D., Morris Rosenberg, Ph. D., George Coelho, Ph. D., Leonard Pearlin, Ph. D., Irwin Greenberg, M. D., Elizabeth Murphey, M.S.W., Fredric Solomon, M. D. Research Assistants: Anne Stephansky, Pam Duncan

Cooperating Units: Laboratory of Socio-Environmental Studies

Man Years (calendar year 1960):
Total: 4.53
Professional: 3.4
Other: 1.13

Patient Days (calendar year 1960):
None

Project Description:

Objectives:

To study the resources healthy adolescents use to cope with the tasks of a challenging life situation. We are exploring in healthy subjects the sources of strength in making the transition from high school to the freshman year of college. We are attempting to define factors in the subject's life history, his family, his personality, and current social milieu that are related to his coping techniques during the period under study.

Method:

This project is an exploratory pilot study of a group of students, selected to meet certain criteria of effectiveness, who were in transition from the senior year of high school through the freshman year of college. Students were selected from a group of volunteers whose high school records indicated effective academic performance, favorable personality ratings by teachers, and participation in extracurricular activities. Following initial screening interviews, students were selected who were regarded as competent academically, in their friendships and in their ability to relate to groups. Fifteen of the students selected for the project met the specified criteria and an additional five students

who showed more overt problems along with other areas of effectiveness while in high school were also studied as a sub group.

These students have attended a wide range of different colleges in the Eastern section of the country. Those selected for study were seen for a series of interviews in the spring of their senior year of high school, during the summer preceding their leaving for college and for interviews spaced over the academic year while in the freshman year of college. The study included a field visit to the student at his college approximately six weeks after he began the freshman year. Students were seen during the Christmas and spring vacation periods and again in June following their return home from college.

A special projective test was developed, patterned after the TAT. This consisted of 11 pictures related to the college experience and was designed to elicit fantasy material about modes of coping with potentially stressful college situations. This test was administered to the subjects in the project prior to their going to college and again during their Christmas vacation after they had been at college. In addition, the test has also been administered to a group of students at the University of Maryland and also to students hospitalized because of breakdown during the college experience, as a basis for making comparisons with our students. At the present Dr. Coelho is pursuing further validation of the test material with students selected in the freshman year at the University of Maryland.

Two interviews were conducted with the parents of each of the students. These interviews were conducted with the parents prior to the students leaving for college and after the students had returned home for the first visit from college. In addition, we conducted a joint interview with each student and his parents in the summer after the end of the freshman year of college to review the year's experience and also to gain some insight about interactional patterns between parents and students.

Some exploratory group interviews were also conducted during the year with a group of eight freshman students at the University of Maryland.

In analyzing the interview material, the following areas were used as units of analysis:

1) The decision to go to college and the choice of college,
2) coping with the anticipation of the transition to college while in high school,
3) the formation of friendships in the freshman year at college,
4) the development of autonomy and the student's relationship with his parents,
5) patterns of dating and heterosexual development,
6) the impact of the academic experience and intellectual values at college,

7) the major developmental issues emerging during the transitional experience, and
8) analysis of the Student Thematic Apperception Test Material.

Patient Material:

Subjects in this study are not patients, but normal subjects who meet certain criteria of effectiveness in their daily living. Forty high school students were interviewed initially, from which twenty were chosen for follow-up. In addition, four high school students participated in a series of group discussions about the Bethesda-Chevy Chase High School.

Eight freshman students at the University of Maryland were selected from a group of volunteers from an advanced English section for a series of group discussions.

Major Findings:

Following is a summary of the major findings of material which has been analyzed thus far:

1. The Decision to Go to College and the Choice of College:

For these students the decision to attend college represents an internalization of parental expectations, rather than a conscious decision per se. However, these students exercise a great deal of autonomy in the choice of particular colleges for themselves. The application procedure involved a process of self-assessment along with an assessment of characteristics attributed to the college. Students tended to select colleges which integrated their parents' values along with their own. When there was disagreement, the parents were able to accept the student's position without a rupture in the relationship. These students adequately coped with rejection experiences during the application process by being able to maintain their self-esteem and viewing this as a learning experience.

2. Coping With the Anticipation of College:

In anticipation of college during high school, these students demonstrated potentially useful personality characteristics: a desire for new experience, a tendency to be active in dealing with the tasks of the transition, and a sense of pleasure in mastery of the challenge. In addition, some of their behavior in high school could be understood as a way of developing a self-image as adequate to the perceived requirements of the new situation [illegible] inference to analogous past experiences, by reference to a [illegible] continuity with the present self, by learning about the new situation in advance, by role-rehearsal, by group identification, by lowering the level of aspiration, and by selectively perceiving encouraging elements in

the new situation. In addition, there were mechanisms for maintaining distress within manageable limits: by recognizing and finding reassurance in the awareness that others shared similar feelings, by attributing useful functions to having concerns about college, by taking action in the present about some anticipated future concerns, and by rehearsing in fantasy how one would deal in the future with some possible contingency. These attitudes of pleasure in dealing with newness, the matching of the self-image with what is expected, and mechanisms for containing distress within manageable limits reinforce one another and provide a general basis for confidence in meeting the situation ahead.

3. The Formation of Friendships in the Freshman Year at College:

We examined the process by which these students coped with the task of making friends at college. By and large they moved rather quickly into the college situation and rapidly involved themselves in the world of their peers. They approached college with a positive attitude about their ability to make friends and a sense of optimism in regard to this, valuing the benefits to be derived from friendships. They used institutionalized resources in becoming acquainted with the college and felt a readiness to involve themselves in the new experience. A number of students experienced a feeling of detachment from old friends in high school, which facilitated a readiness to form new relationships. We identified two phases in the formation of friends. In the early weeks, the task seems to be one of reaching out for those in the most immediate proximity with whom to make friends. These early friendships combat loneliness, meet the need for reassurance that one is going to be accepted and in providing a means for orientation to the new situation. As these needs are met, the students begin to "act more like themselves" and become more discriminating about the basis on which the friendship continues. The secondary phase of friendship changes the basis on which the friendships continue from proximity to the sharing of mutual interests. The functions served by friendships in this phase are varied. A small friendship group tends to coalesce, which provides an important sense of belonging for the student and offers an opportunity for the confirmation of the student's own values. Friendships provide an important vehicle for exploring new identity possibilities. A friendship group may provide stimulation of the student's intellectual development as well. Students learn from each other through pooling of information and through process of role-complimentarity. The friendship group offers support for the student in times of crisis and conflict. Contact with old friends from high school provided a basis for students making comparisons about their particular experience at college and as a way of evaluating change in himself.

4. The Development of Autonomy and the Students' Relationship With Parents:

In regard to separation from parents, our students experienced little difficulty about the immediate impact of the change since most of them had had previous experience with this aspect of the separation. However, the separation from parents provided an opportunity for the further development of the students' autonomy which in most instances coincided with a feeling of continued relatedness with parents. We found it useful to divide our students into groups at the end of the freshman year on the basis of the extent to which they had developed autonomy and the extent to which they felt close to their parents. By including the data from five students who had more apparent problems in high school, we could divide our total sample into four categories: those high in autonomy and relatedness, those low in both, those high in one but not the other. In comparing the student's interaction with his parents among these four categories, we felt we could make generalizations about two of these categories; namely, those students in the high-autonomy, high-relatedness group and those in the low-autonomy, low-relatedness group. The pattern of interaction of students who are high in autonomy and high in relatedness to parents is one in which the parents emerge as distinct people and present a great deal of clarity about their values and standards to the students. These are parents who value and foster the growing autonomy of the child. They can tolerate more experimentation on the part of the child within the framework of the family standards, making it clear that the child will have to assume responsibility if he moves out of this framework. They tend to view the child as ready to take over responsibility for his own life and there is a clear definition of boundaries between the parent and child with a value placed on respecting privacy on the part of the student. The converse of these hypotheses would apply to the parent-student relationships of those students who were described as low in autonomy and low in relatedness to parents.

5. Analysis of Student Thematic Apperception Test:

In analyzing the material obtained from the Student's Thematic Apperception Test, comparisons were made between students in this project, ten University of Maryland freshmen (selected from those who had passed an advance placement test in English) and ten patients who were hospitalized because of severe emotional difficulties experienced in college. Group differences can be noted in three categories of coping behavior for which the students' stories were rated: namely, positive indication of a clear resolution or outcome in the story, positive indication of clearly active efforts produced by the hero in the direction of resolution, and positive indication of a clearly favorable resolution. Students in the Field Study Group and University of Maryland freshmen show a higher frequency of positive ratings on each of these measures than the Ward patients. The Ward group shows lower problem-solving competence, compared to both the

normal subjects. The Ward group produced relatively few clear solutions in potentially stressful college situations and only half of these solutions are favorable. The Ward group in their stories portray the hero as expending proportionately greater effort than the Field Group, only to achieve unfavorable solutions.

Significance to Mental Health Research:

There is a paucity of intensive psychiatric studies of mentally healthy people. Psychiatric research has traditionally centered in the problems of disordered functioning and inferences about healthy functioning have been based, for the most part, on experiences with the mentally ill. This study offers an opportunity to examine adaptive patterns and coping resources in the healthy adolescent faced with a transitional life experience. It may illuminate, further, the kinds of experiences that favor adaptation and growth during the late adolescent period. Mental health research requires a need for understanding more of the constructive aspects of human behavior; those conditions fostering growth along with an interest in the factors and forces that contribute to breakdown in maladaptive behavior.

Proposed Course of Project:

1. A continued analysis of the interview data will continue during this year. We are now engaged in reviewing units pertaining to heterosexual development, the impact of the academic experience and particular developmental issues during the transitional experience. We plan also to review the material obtained from the Student's Apperception Test to see if it is possible to postdict particular coping behavior which we observe by our students in the actual college situation.

2. While the project was focussed on the freshman year experience, we feel that a continued follow-up of this group of students will offer an important source of data about implications of our observations during this period in terms of the students' subsequent development. For this reason, we plan to maintain contact with our students and their parents by interviewing them once a year during the remaining college experience.

3. We plan to follow up our observations about the patterns of parent-student interaction by having further contact with the parents of our students during the summer of 1961 as an opportunity for developing techniques for subjecting our impressions to more critical evaluation.

Part B included: Nos.

Serial No. M-AP(C)-16
1. Adult Psychiatry Branch
2. Section on Personality Development
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: A Study of Problems in Growth and Adaptation in the Personality Development of the Adolescent

Principal Investigator: Roger L. Shapiro, M. D.

Other Investigators: James Maas, M. D., Blanche Sweet, Ph.D., Carl Wolff, M. D., Fredric Solomon, M. D., William Bunney, M. D., Carmen Cabrera, M.A.

Cooperating Units: Nursing Personnel of 3-West

Man Years (calendar year 1960):
Total: 4.5
Professional: 3.0
Other: 1.5

Patient Days (calendar year 1960): 4,015

Project Description:

Objectives:

In the Personality Development Section of the Adult Psychiatry Branch we have been investigating psychological aspects of the developmental process in adolescence. We have been interested in what past and current life experiences facilitate adaptation to the developmental tasks of late adolescence with concomitant personality growth. We have also wanted to understand what factors lead to failure of adaptation, growth inertia, or regression in late adolescence and what can be done about these problems.

Methods Employed:

We have approached the study of personality development in late adolescence by selecting a widespread and significant task of that developmental phase and studying individuals who manifest disturbance in their efforts to accomplish this task. The task we have selected is that posed by the requirements of the transition from high school to college. We have accepted as patients for our study young people who have had sufficient emotional difficulty during their freshman year at college to make it necessary that they drop out of school. We have conceived of the adjustment to college

containing many of the developmental tasks of late adolescence, which make demands upon the adaptive capacities of the individual in a number of areas. Among these tasks are: separation from parents and living away from the family for a prolonged period of time; living primarily with peers and having more significant relationships with peers; the demands of increasingly intense and mature patterns of sexual expression; the increasing intellectual demands of college work; an increasing requirement for decisions relating to vocational choice. We want to determine what current and past social experience interacts with the individual potentialities, to encourage the adaptive capacity of the individual in his mastery of the tasks of this phase, conceptualized by Erikson in their most generalized form as the achievement of a sense of ego identity. We want to understand what is lacking or inhibiting in the particular life experience of the individuals we study, both currently and in the past, to interfere with the realization of their potentialities in late adolescence. Finally we want to utilize our therapeutic program in a way which will help us to understand what aspects of current social experience can encourage realization of potentialities previously interfered with and allow for further personality development. We are concentrating our investigative efforts in two broad areas in our attempts to answer these questions. We are studying the recent situation in which the patient experienced acute difficulty, the developmental task with which he was confronted in college; and we are studying the family experience of the individual.

Our efforts to study the college experience of our patients has taken three major forms. Each of our patients is interviewed by one of the investigators in a series of research interviews which follow a schedule of areas of particular interest to us. Questions are asked in the following areas: What was involved in the decision to go to college; in the emotional preparation for college; in the initial adjustment to college; in friendship formation in college; in the reaction to the academic challenge; in other areas of difficulty in adjustment; in various reactions to these difficulties; in the crisis and the departure from school. A second source of information about the college experience is contained in the picture obtained in psychotherapeutic work with the patient of what his college experience was. This is organized and written up by the therapist in a form covering the same areas of interest as the research interviews so that they can be compared. A third source of information about the college experience is a visit made by one of our investigators to the college in which the patient had difficulty, to interview friends, teachers and advisors of the patient in an effort to gain another vantage point for viewing the nature of the psychosocial environment with which the patient had to deal, adaptive efforts he made to the situation, and the nature of the relationships he formed. The patient's picture of these adaptive efforts and relationships is compared with the picture of those who have gone.

Our effort to study the family experience of the college [illegible] in the past six months resulted in our utilizing the [illegible] the patient, his parents, an adolescent sibling i[illegible] of the patient, and the social worker. These sess[illegible]

weekly and are observed by two investigators. They are integrated into our therapy program, which also includes two individual sessions a week for the patient with his psychotherapist, an individual session a week for the parents with the social worker, and two sessions of group therapy per week for the patients.

We attempt to utilize interviews where family interaction can be observed, to shed light on the identity question in the following way: We pay particular attention to the interaction between parents and patient which gives some indication of the way in which the parents overtly and covertly identify the patient and the way in which he overtly and covertly identifies the parents. If we can see demonstrated relatively rigid and enduring delineations of the patient by his parents, which make for inflexibility in his sense of identity and anxiety over the changes in the concept of himself which the developmental phase requires, we will understand more of what contributes to pathological outcome in the period of identity crisis. We look also for evidence of inflexibility and stereotyped expectation on the part of the patient in the manner in which he delineates his parents, and unconsciously keeps them in stereotyped and rigid roles. With this identity question as the central focus of our research interest in the family sessions, we report on this aspect of the interaction in two ways. The therapist makes it a part of his summary of the interview; and observers follow each interview from this point of view rating on a prepared form short sequences in the interview which reveal parental expectations of the patient and patient's expectations of the parents, delineations back and forth of what they can allow into their concept of the other. This includes their conscious statements about the other person; it also includes affective behavior toward the other person from which unspoken or unconscious attitudes can be inferred. We have 2 observers recording independent impressions in an effort to arrive at reasonably objective findings.

Major Findings:

This investigation into problems in the personality development of the late adolescent has been in progress since January 1959. In these two years we have hospitalized nineteen college students, predominantly freshmen, who were in sufficient emotional difficulty to make it advisable that they leave school. Interviews with these students about their college experience allow generalizations to be made in a variety of areas. We have summarized the data from interviews of 10 of these students under the following headings and are now analyzing the remainder along these lines:

1. Attitudes toward new situations and change; 2. Manner of arriving at the college decision; 3. Dating and sexuality; 4. Order, organization and control; 5. Friendship patterns at college; 6. Career studies, intellectual achievement, as a problem.

Significance to Mental Health

We are currently making an effort to elucidate those interactions between parent and adolescent which in part determine the adolescent's feeling about what he is able to do, and what he is free to become. As we understand more fully what experiences within the family inhibit the adolescent in the development of his potentialities we hope to be able to make a contribution to the theory of therapy of disorders late adolescence. We have some indication that the usefulness of family sessions in the therapy of late adolescent disorders may be a significant contribution of our program. We also hope that understanding we achieve of disturbances of ego identity in late adolescence will suggest directions for programs for promoting mental health in late adolescence.

Proposed Course of Project.

In the next year we plan to continue detailed examination of the interactions within the families of our patients and the manner in which the delineations of the adolescent by his parents and of the parent by the adolescent determine the ego identity of the patient and play into the adaptive difficulty he has manifested in facing the developmental tasks of the late adolescent phase of personality development. We will continue our investigation of this psychosocial phase as it is exemplified in the tasks involved in adjusting to the college experience, and attempt to further understand what sorts of experience might facilitate adaptation in this phase, and what in our program of therapy promotes further growth in the individual who has experienced difficulty.

Part B. included: No

Serial No. M-AP(C)-18

1. Adult Psychiatry Branch
2. Section on Psychosomatic Medicine
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Biological Studies of Sleep and Dreaming (Formerly "Sleep and Dreams in Relation to Blood and Urine 17-Hydroxicorticosterone Levels")

Principal Investigator: Frederick Snyder, M.D.

Other Investigators: David A. Hamburg, M.D.

Cooperating Units: None

Man Years (calendar year 1960) Patient Days (calendar year 1960)

Total:	0.9
Professional:	0.8
Other:	0.1

Project Description:

Objectives:

To investigate the physiological and psychological concomitants of sleep and dreaming in an effort to further define and quantify their parameters. In its present phase the project takes the form of a series of small scale, hypothesis seeking, exploratory studies.

Methods Employed:

All night records of electroencephalographic, electrooculographic and various other physiological measures, such as respiration, heart rate, plethysmogram and skin temperature are obtained from sleeping subjects. Details of the procedure have varied among the sub-projects through which the study has progressed. For some purposes the recording has been done without disturbance of the subjects' sleep, and for other purposes subjects are systematically awakened by means of graded sound stimuli, at which time they attempt to describe their subjective experience prior to awakening, including whatever dream sequences they can recall.

Patient Material:

The subjects employed have been normal volunteer controls.

Major Findings:

1. Three types of observations reported by other investigators have been repeated and essentially substantiated:

   (a) Dream recall is associated with a particular patter of electro-encephalographic and eye movements.
   (b) There is a regular and invariable recurrence of this physiological pattern three to five times in each night of sleep, taking up an average of 20% of the total sleep time.
   (c) Interruption of sleep at the onset of this pattern over a series of consecutive nights leads to a progressive increase in "dream attempts", and the nightly "dream time" is markedly elevated for several nights after the conclusion of the "dream deprivation" period.

2. Several aspects of these phenomena which had not been mentioned in previous reports were noted:

   (a) A high degree of variability was found in the incidence and vividness of dream recall among subjects, in the same subject from night to night, and over the several dream periods of a given night.
   (b) There is a considerable range in the percentage of sleep time taken up by "dream sleep", to some extent apparently the expression of individual differences, but to a larger extent taking the form of night to night variation in the same subject.

3. An attempt to account for some of the variability in percentage "dream time" through a hypothesized correlation with 17-hydroxy-corticosterone levels was not supported. Nor was it possible to demonstrate a relationship between this endocrine measure and the "threat" quality of manifest dream content (Project No. M-AP(C)-18). Although these were the original objectives of the project, it was decided to leave these questions in abeyance pending further investigation of the parameters of the sleep and dream phenomena.

4. The revised objective of the study became that of attempting to find physiological parameters of "dream sleep" which would relate to the vividness of dream recall. It was considered feasible to combine this objective with that of a re-examination of the question of sleep "depth". To these ends two additional facets have been explored.

   (a) Auditory thresholds for awakening and for signs of physiological arousal short of awakening have been obtained during various [illegible] stages of sleep, and in connection with the subject's rating of the vividness of his dream memories. In agreement with the reports of previous studies, the auditory [illegible] revealed a fairly predictable relationship between the [illegible] and the

intensity of stimulus required for awakening outside of the "dream sleep" periods. It was noted, however, that this relationship was a relative one, with considerable variation in the absolute levels of stimulus required among subjects or in the same subject under different conditions of "sleep need". Hence, it appears that the EEG pattern is not an absolute index of sleep "depth" as defined in terms of arousal thresholds. Within the periods of "dreaming sleep" the intensity of awakening stimulus was extremely variable, with no constant relationship to thresholds required during other EEG stages, per to the vividness of dream recall.

(b) Physiological variables other than the EEG and eye movements have been monitored in the hope that they would provide indices which would relate to the vividness of dream recall, or to the depth of sleep as determined by arousal thresholds. Thus far these have included heart rate, respiration, plethysmogram and skin temperature. This resulted in the finding that all of these measures tend to distinguish between "dreaming sleep" and "dreamless sleep", particularly in terms of the much higher degree of minute to minute variability of the measure during dreaming. This is especially striking with regard to the variability of respiratory rhythm. Early results are quite encouraging that this measure may relate to the vividness of dream recall. If further work bears this out, we will feel justified in postulating a parameter of "dream intensity".

In relation to sleep depth, each of the autonomic measures is at least roughly related to the EEG stages of sleep. Whether any of them might be a better absolute index of sleep "depth", as measured by arousal thresholds, remains to be studied.

Significance to Mental Health Research:

In striking contrast to the apparent importance of sleep and dreaming in human life is the dearth of established knowledge concerning these phenomena. Far from understanding the nature of their psychophysiological functions, we are lacking even in adequate physiological description of them. It is evident that sleep is not a uniform state from hour to hour in the same night, from night to night in the same individual, or from one individual to another. There is reason to believe that the same is true of the physiological substrate and of the subjective experience of dreaming. Yet, the parameters of such variability have yet to be conceptualized and made amenable to measurement. Only then will it be possible to make quantitative studies of sleep and dreaming in relation to the organismic economy. In view of the well known, and apparently universal association of disturbed sleep and mental illness, it seems reasonable that attempts to define and quantify the parameters of sleep might eventually lead to important clinical implications.

Proposed Course of Project:

In addition to continuing data collection and analysis [illegible]

described, the following are seen as possible lines of development of the project.

1. Inclusion of further physiological measures, such as blood pressure, skin resistance, gastric activity, and such blood chemicals as glucose, epinephrine, and nor-epinephrine.

2. A comparison of the type of data described from normal subjects with parallel observation from various psychiatric groups. This has already begun on a small scale in the form of a collaborative study with the Clinical Neurophysiology Research Center of sleep and dreaming in acute schizophrenic subjects.

3. An attempt to relate enduring individual difference in dream recall and nightly dream time to enduring differences in the concomitant autonomic measures.

Part B. Honors and Awards Relating to this Project:

Snyder, F. "The Question of an Invariant Dimension in Dreaming", Symposium on Dream Research, Annual Meeting of the American Psychiatric Association, May 12, 1960.

Snyder, F. Discussion, paper by Dr. William Dement, "Studies of Sleep and Dreaming", Meeting of the Washington Psychiatric Association, September 28, 1960.

Serial No. M-AP(C)-19

1. Adult Psychiatry Branch
2. Section on Psychosomatic Medicine
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Relation of Emotional Behavior and Endocrine Function

Principal Investigator: David A. Hamburg, M.D.

Other Investigators: John Mason, M.D., Jacob Fishman, M.D., William E. Bunney, M.D., Stanford Friedman, M.D., James Maas, M.D., Joseph Handlon, Ph.D., Edward Sachar, M.D.

Cooperating Units: Walter Reed Army Institute of Research, Department of Neuroendocrine Research; Laboratory of Clinical Sciences and Laboratory of Psychology, NIMH; Nursing Staff, Clinical Center, NIH.

Man Years (calendar year 1960)		Patient Days (calendar year 1960)
Total:	7.	
Professional:	5.	4,320
Other:	2.	

Project Description:

Objectives of Research on Minor Stress:

In our Section on Psychosomatic Medicine, we have been investigating some endocrine correlates of mild psychological stress. For the most part, stress studies have centered on critical, high distress, emergency-like conditions. We too are pursuing such studies. However, we believe that the minor stresses of ordinary living require investigation also. While endocrine responses under everyday circumstances are likely to be less striking than under emergency conditions, they may nevertheless have considerable long-run significance for the human organism. These studies of mild stress, including work on relief of moderate tension, have been conducted with young adult volunteers.

Methods Employed:

During the past year six groups of normal volunteer subjects have been resident on Ward 4-East for periods of time ranging from nine to

fourteen weeks. All of these subjects have been here primarily to participate in psychoendocrinological studies. In general these involve the relations between endocrine function, normal variation in emotional states, and a variety of psychological stresses both induced and occurring spontaneously. A major part of this program of research involved the creation of a fairly normal and standardized living situation within the hospital environment in which a variety of stable psychological and endocrinological observations might be obtained. This is an attempt to form out of the living situation itself a research instrument that might be used for different groups of subjects at different times but be reasonably stable and consistent for comparison of data. We are studying the phenomena of adaptation to this new environment which presents many ambiguities to the entering volunteer. In addition to acting as subjects the volunteers participate in a variety of work-project jobs ranging from those of lab technicians to secretarial work. The subjects keep a daily diary of experiences and thoughts and a daily mood check-list. The head nurse maintains a weekly 'problem seminar' directed at specific nursing problems. A well functioning system of routine urine collections has been worked out and nursing staff fills in a weekly set of psychological ratings for each subject. The categories of psychological observations on these lists have been developed with the collaboration of the staff so that consensual validation of categories (e.g., depressed) has been maximized. Frequent discussion and re-evaluation helps maintain a high level of inter-observer reliability. The week of admission to the Clinical Center has provided us with an opportunity for analysis of behavior-hormone relations under mild stress. So far we have studied six groups of normal volunteers, comprising seventy-two individuals.

In the past, studies of the endocrinological effects of environmental stimulation have almost invariably focused upon the ability of a particular situation to bring about an increase in the circulating levels of certain hormones. Little or no attention has been paid to situations which may consistently lower such endocrine levels. In our Section on Psychosomatic Medicine, we have been attempting to develop experimentally controllable situations of mild stress, and have discovered several conditions which led to the lowering of plasma hydrocortisone concentrations.

Using young (18-25 years) normal volunteer adults of both sexes who spend several months living on the wards at the Clinical Center of the National Institutes of Health, attempts were made to determine if the showing in a group situation of certain selected commercial movies judged to be emotionally "arousing" could bring about consistent increases in plasma hydrocortisone concentrations. As control films, several Disney nature films were also shown. Bloods were drawn from the subjects prior to the showing of the films and immediately afterwards. In addition, self-assessment of mood was obtained from each subject by

a modification of the Nowils-Green adjective check list before and after the showing of the films.

In order to control for the showing of either arousing or bland films, a second group of all young adult males had, in addition, bloods drawn during a comparable control period during which time the subjects followed their usual activities on the ward.

Findings:

For most of the normal volunteers, there was an initial preoccupation with NIH, some concern about possible risks, and moderate tension on the day of admission. This was usually followed by a rapid adaptation characterized by active exploration of the new environment, increasing familiarity, encouraging personal relationships, and diminishing tension. For most subjects, this adaptation was largely accomplished by the end of the first week. For five of the six groups, psychological stress was largely absent during the remainder of their stay. All five of these groups (n=60) showed steady decline in corticosteroid and catechol amine excretion during the initial 1-2 weeks and stabilized thereafter. However, one group (n=12) was brought in under fundamentally different psychological conditions. These were marginal students in a local university, experiencing financial and academic difficulty. For them, the opportunity of living in the Clinical Center for two months while preparing for final examinations was a favorable circumstance, since it relieved them of financial pressure for the time being. They were, however, under stress as the examinations approached; distress was in the mild-to-moderate range. Interestingly, this group differed sharply from all other groups in patterns of adrenal hormone excretion. Whereas all five other groups showed diminishing excretion of corticosteroids and catechol amines during the initial week in the Clinical Center, this group went up sharply as soon as the students returned to school (after a one-day orientation at NIH) and remained consistently high thereafter. We were also able to get considerable data on additional endocrine variables, especially estrogen and androgen excretion, during final examination periods.

The difference in the mean pre-to-post-film changes in plasma hydrocortisone concentration for "bland" vs. "arousing" films is highly significant. The change in subjective mood accompanying either "bland" or "arousing" films corresponds to what might be expected from the nature of the stimulus. For those subjects for whom control levels were also obtained, there is again a drop in level during the showing of bland films, with only a slight increase in levels during the showing to "arousing" films. The control period shows a drop that is appropriate in terms of diurnal cycle.

Project Description of Research on Major Stress:

In the latter part of the year we began three new major stress studies in the neuroendocrine field. The primary stimulus for these studies is our ability to measure several additional hormones: (1) urinary excretion of androgens and estrogens; (2) blood levels of butanol-extractable iodine as an index of thyroid function; (3) blood and urine levels of aldosterone. We are interested in determining whether these hormones will be affected under conditions that have already been shown to be associated with elevated blood level and urinary excretion of hydrocortisone, epinephrine, and norepinephrine.

The first of these major stress studies is being done through the cooperation of Dr. Gordon Zubrod and his staff in the National Cancer Institute. Dr. Stanford Friedman and associates are doing a study of coping behavior in parents of leukemic children and making serial hormone measurements over a period of several months on each parent. The second study, under the leadership of Dr. James Maas, involves serial hormone measurement in patients admitted to our unit for disturbed college students. Similarly, the third study, under the leadership of Dr. William Bunney, involves serial hormone measurement in patients admitted to the Clinical Center because of severe depressive reactions. In the latter two studies, the investigators are working closely with nursing staff to develop systematic observational techniques for rating of behavioral variables.

In most of our psychosomatic research, we are collaborating very closely with the Department of Neuroendocrinology in the Walter Reed Army Institute of Research under Dr. John Mason. Similarly, Dr. Joseph Handlon of the Laboratory of Psychology has been an active collaborator in most of these studies. Also, in several recent projects we have been collaborating with members of the Laboratory of Clinical Sciences: Dr. Philippe Cardon and Peter Mueller in measuring free fatty acids in relation to emotional distress; and Dr. Roger McDonald and Mrs. Virginia Weise in measuring VMA as an index of adrenomedullary function in depressed patients.

Outline of Project on Endocrine Function in Severe Depression:

The present project on 3-East is a study in which there will be an attempt to correlate various psychiatric aspects and characteristics of depression with the level of certain hormones in the blood and urine. The psychological aspects and variables of depression to be studied will include severity of illness, degree of retardation of the patient, amount of psychotic behavior and the diurnal changes seen in the patients. Epinephrine, norepinephrine, VMA, hydrocortisone, aldosterone, sex hormones, Butanol-extractable iodine and pepsinogen will be measured chemically. The patterns of response shown by these hormones will be correlated with the changes in the depression of the patient. This work was stimulated by a number of previous projects. The most significant of these are: (1) The work by Hamburg, Board,

Persky, et al, which showed very high hydrocortisone levels in severely depressed and retarded patients. (2) Preliminary work done by McDonald and associates at NIH on VMA (a breakdown product of norepinephrine and epinephrine which is excreted in the urine) which showed elevated levels in four involutional melancholia patients. (3) The work of Mason and associates in developing biochemical methods for analysis of hydrocortisone, epinephrine, norepinephrine, aldosterone, thyroxin, estrogens, and androgens.

Procedures:

A. Evaluation of the patient's mood. This will be done by three groups, the nursing staff, the patient himself and the physician. The nursing staff makes out a 41-item mood check list on each patient during each day and afternoon shift. Toward the end of each day and evening shift, the nursing team makes a consensus summary of the patient's mood during the day, and the nursing team also makes a consensus rating for each patient and plots this rating on a graph of depression. The patients keep daily diaries and rate their own moods as to the degree of depression experienced during the day. The physician rates the patient on the mood check-list within the first 24 hours after admission and also at the time of discharge. The rationale for the gathering of data by nurses follows: First, the nursing team makes out the mood check-list on each patient. This helps each member of the team review in his own mind the various important components of depression that the patient may show during the shift. There are six scales built into the check-list - anxiety, anger, psychotic behavior, manic behavior, an improvement scale and a scale for depression. The first five scales help the rater contrast the depressive behavior with other types of behavior and, therefore, may etch more clearly the depressive aspects of behavior of the patient during the shift. It also constantly familiarizes the rater with various aspects of depression. Following this the nursing staff makes a summary of their impressions of these rating sheets and of the patient during the shift. This is the consensus summary and this is followed by plotting the patient on a graph of depression.

B. (1) There is a continuous collection of all urine from each patient during their total hospitalization. (2) Samples of blood are drawn periodically from all patients at 8:00 a.m. and 8:00 p.m.

C. Each week the material about the patient's mood is analyzed and a decision is made as to which days will be selected during the week for chemical analyses. For example, the worst and the best days during a week for each patient may be selected. The urine collected on that day for a particular

patient will then be sent to the lab for chemical analyses of the various hormones.

Outline of Study on Fatty Acid Mobilization in Depressed Patients:

It is now established that increased plasma concentration of free fatty acid (hereafter referred to as FFA) occur in acute states of arousal (fear) in normal volunteers. The first work in this field has been published by Cardon and Gordon (J. Psychosomatic Res. 4: 5, 1959), and Bogdonoff (Proc. Soc. Biol. & Med. 100: 503, 1959) also presented further data at American Psychosomatic Society in 1960. Some work now in progress on 4-East at NIMH by Drs. Mueller and Fishman would suggest that acute anger can also cause an increased rate of FFA mobilization. It is probable that the well-known effect of epinephrine on fatty acid mobilization (reported by D. S. Fredrickson and R. S. Gordon, Jr. in Physiol. Revs. 38: 585, 1958) is involved in these acute states. There are no published studies on the plasma level of FFA in psychiatric patient populations. Some studies of chronic schizophrenics are now in progress on 2-East at NIMH. It is of some interest, therefore, to study the effects of the extremes of depressive affect and symptomatology upon plasma FFA concentrations. It must be noted, however, that elevations of plasma FFA concentration occur in hypermetabolic states (Hyperthyroidism), diabetes, and starvation. Therefore, in order to eliminate artifacts, each patient should have a P.B.I. and fasting blood sugar and be on an adequate diet. Thirty calories per Kilogram of patient body weight would be the minimum diet control. It would be preferable that this intake be consumed for two days prior to drawing the fasting morning blood sample for FFA determination. Eight ml. of blood is drawn before breakfast, placed in a pearinized test tube, and sent to Dr. Mueller on ice. Psychiatric observations will be noted on each patient for the 48-hour period prior to and including the drawing of the blood, as well as relevant diagnostic data about the patient's personality. The plasma FFA concentration will be determined in Dr. Mueller's laboratory. This procedure may be repeated on each patient several times during his hospital stay, depending on his psychiatric status.

Outline of Study on Endocrine Function in Parents of Leukemic Children:

The plan is to study the parents of the hospitalized children with leukemia. Though the fact that these parents are under continuous stress in self-evident, the nature of the stress and the adaptation process undoubtedly change as their child's clinical condition fluctuates and varying past and present experiences exert their influence. We have formulated an interview schedule, outlining the areas we wish to cover with the parents. We are principally trying to delineate coping behavior and emotional responses. We interview parents of new admissions, explaining to them that we are interested in how they have been able to work with the doctors in the overall management of their

child. At the end of the first interview, or even at a later time, further explanation of the study could be given with the request for a limited number of blood and/or urine specimens. The first interview should optimally be within 24 hours after admission, if this does not interfere with other routines. Interviews then at rate of 1-2 per week. Some of these parents are admitted to the "normal volunteer" floors of NIMH. We have worked out rating for anxiety, depression, hostility, and denial. Fluctuations in these variables are related to fluctuations in hormone levels. We have also worked out criteria for various categories of coping behavior.

Outline of Study on Endocrine Function in Emotionally Disturbed College Students:

The patients will all be taken from the college student project. This sample offers the advantage of consisting of subjects who have had demonstrated difficulty in handling stress situations and furthermore some of these patients during their stay on the ward will show particularly wide swings from relative well-being to severe disturbance. All new admissions will have hormone determinations done on the day of admission. Those newly admitted patients who are moderately to severely disturbed and who seem to have a good likelihood for psychological reconstitution during the first four weeks of admission will have serial daily hormonal determinations done. An attempt will be made to "pick up" on patients who may be in the process of developing a severe disturbance and these patients can be followed serially (daily hormone determinations) from well-being to severe illness to well-being.

Significance to Mental Health Research:

Stress research increasingly suggests that the anticipation of personal injury, whether it be physical or psycho-social in nature, may lead to important changes, not only in thought, feeling and action--but also in endocrine and autonomic processes, and hence in a wide variety of visceral functions.

In recent years, much interest has been centered on the adrenal cortex in relation to psychological stress. Stimulation of certain brain areas produces major changes in circulating concentration of hydrocortisone, one of the principal adrenocortical hormones. Stimulation of the infundibular portion of the hypothalamus in rhesus macaque produces marked elevation of plasma hydrocortisone levels, whereas control stimulation in the putamen or anterior thalamus does not. Functional relationships between two limbic system structures and the pituitary-adrenocortical system have been described. Stimulation of the amygdaloid nucleus produces a maximal increase in pituitary-adrenocortical activity. The hippocampus-fornix system appears to be capable of exerting an unusual, prolonged

suppressive action on the pituitary-adrenocortical system. With respect to behavior, certain stressful experimental procedures produce sharp increases in plasma hydrocortisone. Both a conditioned fear situation and a conditioned avoidance situation are associated with similar marked increases in plasma hydrocortisone levels which were as great as those observed following injection of a large dose of adrenocorticotrophic hormone. Since the introduction of a precise, reliable biochemical method for measuring hydrocortisone by Nelson and Samuels in 1952, several laboratories have undertaken major studies of plasma hydrocortisone concentrations under naturally-occurring stressful conditions in man.

In aggregate, 269 individuals have been studied in several laboratories under conditions of fairly intense distress. These groups consistently show mean plasma hydrocortisone levels around 20 mg/100 ml in early morning (between 8 and 9 a.m.). Extensive control studies in the same laboratories of healthy individuals experiencing little or no distress have shown mean plasma hydrocortisone levels of 12-13 mg/100 ml at the same time of day. The differences between these levels and those of the distress groups are highly significant statistically. The measurement of urinary corticosteroid excretion under psychological stress has also been a matter of considerable interest. Several groups have investigated this problem under naturally-occurring stressful conditions.

Data are available on 87 individuals under conditions of personal threat, sustained tension, and in some cases fairly intense distress. These individuals were studied in nine different groups at five institutions. Each of these studies shows higher 24-hour urinary excretion of corticosteroids under stress conditions than under nonstress conditions. These differences are quite significant statistically.

Modern methods of measurement have been applied most extensively to hydrocortisone under conditions of psychological stress. However, there is a growing and intriguing body of work with newer methods on three other adrenal hormones: epinephrine, norepinephrine, and aldosterone. There is now considerable evidence to indicate increased urinary excretion of these three hormones under conditions of fairly intense emotional arousal and distress.

The evidence very briefly summarized here indicates that emotional disturbance in man is associated with elevated blood levels and urinary excretion of adrenal hormones. The most reasonable interpretation of these elevations is that they reflect increased secretion of its four principal hormones by the adrenal gland. This increase in adrenocortical activity is associated with a wide variety of stressful conditions and emotional responses. These studies indicate that

increased adrenal activity may be associated not only with stresses that directly threaten the physical survival of the subject but also stresses that threaten his self-respect or crucial human relationships.

The most recent research in this field suggests increasingly that the endocrine changes accompanying psychological stress are more pervasive than had been assumed previously. In view of the biological potency of these hormones--including notable effects on metabolism of carbohydrate, fat, protein, water, and electrolytes, as well as feedback effects upon the brain itself--these stress phenomena may have a significant part in pathogenesis of psychiatric and medical disorders. With increasing knowledge of basic stress psychophysiology, greater application to clinical problems may reasonably be anticipated in the next few years.

Proposed Course of Project:

The work on minor stress of ordinary living conditions will be fully analyzed and reported during the coming year. The various studies on major stress are in a phase of intensive data accumulation and will be pursued essentially as described throughout the year.

Part B. Included No

Serial No. M-AP(C)-20
1. Adult Psychiatry Branch
2. Section on Psychosomatic Medicine
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Relation of Hypnotically-Induced Emotional Responses and Adrenal Function

Principal Investigator: Jacob R. Fishman, M.D.

Collaborating Units: Department of Neuroendocrinology, Walter Reed Army Institute of Research, Laboratory of Clinical Research, NIMH

Man Years (calendar year 1960)		Patient Days(calendar year 1960
Total:	0.5	80
Professional:	0.5	
Other:	.0	

Purpose:

This work was undertaken approximately eight months ago as part of a general inquiry into suitable techniques for experimentally producing emotional responses and measuring concommitant hormonal changes in normal subjects. It was hoped that hypnotic suggestion would serve to produce specific reliable, and observable emotional responses that might be stimulated and terminated within a specified period of time, the emotions might be analysed for content and intensity by standard psychological techniques, and parallel hormone changes obtained by urine and blood sampling at crucial points in the course of the study. The effective and safe manipulation of such variables in normal human subjects is exceedingly difficult and it was hoped that hypnosis might provide such a technique.

Although some preliminary studies of this nature have been done recently (notably those by Dr. Harold Persky and his associates at the Indiana University Medical Center) we felt it necessary to spend considerable time developing a reliable and suitable experimental design for our purposes. Our techniques for hormonal sampling and analysis have been reliably worked out in the course of our other related studies. On the other hand, however, we have been spending part of our time inquiring into the nature of hypnotic suggestion and resultant affect presenting as it does in its own

right an increasingly interesting and legitimate area of research. We have been most fortunate in having the assistance of Dr. Seymour Fisher of NIMH who has had considerable experience in this latter area.

Procedure:

We have evolved a general design that we have used in studying a variety of hormone changes under several hypnotic conditions. The hormones include 17-hydroxycorticosterone, epinephrine, and nor-epinephrine (with the cooperation of Dr. Mason and Dr. Sachar of Walter Reed Army Medical Center) and also Unesterified Fatty Acids (with the participation of Dr. Peter Mueller of the Laboratory of Clinical Science-CI NIMH). The latter substance has been reported in work by Dr. Mueller and Dr. Phillippe Cardon of our Institute to increase its levels in the blood in response to emotional stimuli. The hypnotic conditions include the state of 'hypnotic relaxation', anger, depression, and anxiety. The affects are 'suggested' either directly (e.g. "You are feeling angry") or by reconstructing an experience in the life of the subject that had produced the affect before (determined in interview before undertaking the study).

Volunteer subjects are obtained from among those normal volunteer college students residing on Ward 4-EAST and participating in AP-19 providing us with additional psychological and endocrine data in a variety of situations with which to compare results). They are screened for susceptibility to hypnosis utilizing a fairly standardized and quantifiable scale (The Stanford Scale). Until now we have been using only those subjects found to be most susceptible but future plans include using less susceptible subjects for comparison. Rorschach testing and interviewing are done on each subject to obtain some insight into individual personality variables and for possible use in reconstructing past experiences.

The hypnotic state is induced by standard techniques. Venous blood samples for hormone analysis are taken from antecubital veins with the use of a cournand needle to minimize the effect of blood-drawing. Standardized interviews are done before each hypnotic session by a person other than the hypnotist to determine the subject's 'base-line' feelings, concerns, anticipations, etc., and after to determine the experiences during the trance and to obtain his subjective reaction to the affect, both as to intensity and content. The suggestion is given to the subject before termination of the trance that he will recall everything that happened. Much attention is given in these interviews to fantasies, associations, and feelings toward the hypnotist (who is not present at the time). In addition the subject fills out an Adjective Mood Check List similar to those used for AP-19 and with which the subject is familiar. One before the trance begins, one for feelings during the affect induction, and one for the post-trance period. The interviews (done by Mr. Victor Stoeffler of NIMH) are analyzed for content and intensity of change and the check-lists quantitatively analyzed for mood change. During affect suggestion two independent observers enter the room (unknown to the subject)

and make quantitative ratings as to 'objective' behavioral changes observed.

Because of the differences in time taken by the steroids, catechol amines, and unesterified fatty acids to respond to stimuli, and because normally plateauing levels of these substances (for reliability of such stimulus studies) in the blood occur during different times of the day (8:00 to 11:00 A.M. in the fasting state for UFA and 12:00 to 5:00 P.M. for the others) these studies must be done separately. Ideally, for each of these studies the subject participates in four consecutive sessions, each on separate days. One session for each of the three affects, - anger, depression, and anxiety, and one 'control' session in which the subject remains in a 'relaxing' trance throughout the session without affect suggestion for possible effects of the trance itself. A typical session for UFA sampling follows:

Blood Samples (7cc)	Time	Activity
# 1	9:00 A.M.	Insertion of Cournand needle. Interview Mood Check List.
# 2	9:15 A.M.	Induction of trance with suggestion of relaxation
# 3	9:30 A.M.	Affect Suggestion (continued for 20 minutes)
# 4	9:40 A.M.	
# 5	9:50 A.M.	Terminate affect. Suggestion of relaxation
# 6	10:00 A.M.	
# 7	10:10 A.M.	
# 8	10:20 A.M.	Terminate trance. Interview #2 Mood check list #2 & #3
# 9	10:30 A.M.	End session.

Discussion:

Our work is really just beginning. Even the few results obtained to this point have yet to be substantially analyzed. It seems pertinent therefore to outline our goals and mention some of the trends that seem promising.

1. Production of reliably reportable and measureable affect through standard hypnotic suggestion. This has been quite successful. Both by direct suggestion and past experience reconstruction we have been able to consistently produce intense anger, anxiety, depression, and marked relaxation. Whether this affect is any different qualitatively or quantitatively from that experienced in 'spontaneous' situations remains an intriguing, important, but unanswered question. Some individuals seem able to produce one affect more readily or intensively than the other affects suggested. The intensity of the affect can only be judged in terms of the observed behavior and subjective reporting. From this it would seem our subjects have experienced remarkably intense emotions. We have been attempting to relate these to factors of personality, accompanying ideation, and transference (to the hypnotist), and expectation.

2. Induction of changes in hormone variables by means of affect suggested in the hypnotic state. In some of our subjects we have produced quite dramatic UFA and 17-hydroxycorticosterone blood increases in a variety of affect states. In others there has been no perceptible change in spite of marked subjective and objective emotional responses during the study. We are at present trying to isolate the possible variables responsible for this remarkable difference.

3. Relate patterns of hormone change to different affect states in hypnosis and to the 'relaxing' trance itself. We have very little information about the former relationship. As to the latter we are fairly convinced. that under some conditions of 17-OH and UFA elevation due to emotional stimuli hypnotic suggestions of relaxation and calm can produce a significant drop in the blood levels of these substances. There has been little attention paid to this descending part of the "stress curve" and the conditions that facilitate it. It would seem to warrant futther exploration.

We feel this preliminary work has been sufficiently fruitful as to invite further expansion and exploration, and that the hypnotic technique will prove a most valuable tool in psychosomatic research.

Part B.

AWards and Honors----NONE

Serial No. M-AP(C)-21
1. Adult Psychiatry Branch
2. Section on Personality Development
3. Bethesda, Maryland

PHS-NIH
Individual Project Report
Calendar Year 1960

Part A.

Project Title: Comparative Study of Problem Resolution in College Students in Research Procedure of NIMH

Principal Investigators: Charmian Elkes, M. D. and Margaret J. Rioch, Ph. D.

Other Investigators: Arden Flint, M. D., Blanche Sweet, Ph. D., Ruth Newman, Ph. D., Nathene Loveland, Ph. D.

Cooperating Units: Eight Guest Workers

Man Years (calendar year 1960):
Total: 2.8
Professional: 1.8
Other: 1

Patient Days (calendar year 1960):
None

Project Description:

Objectives:

The objectives of this project are two-fold, 1) to explore ways of alleviating the shortage of trained workers to provide low-cost mental health services and 2) to fill the gap between two projects already in progress in the Adult Psychiatry Branch on the problems of growth and adaptation in the personality development of the adolescent by investigating the group of students whose adjustment to school or college is marred by disturbances not severe enough to cause an actual breakdown.

These two objectives are being pursued at one and the same time by training a group of eight guest workers as Mental Health Counselors to interview students. In this process information will be gathered bearing upon the second objective. The idea behind the training is that just as the Public Health nurse can perform many duties with and for patients which free the medical officer for the more difficult tasks requiring greater training, so a corps of workers might be trained in the Mental Health field

to deal with the simpler problems, thereby freeing the psychiatrist to treat the more severely disturbed patients. There are probably many people in the community who have aptitude for this kind of work but are not trained for it. One reservoir of such people consists of married women who around age 40 are looking for a constructive activity outside the home to take the place of child rearing. We wish to determine whether such women, if carefully selected, can be trained within two years to perform Mental Health Counseling. In this investigation, the area will be the problems of late adolescence and young adulthood. One of the main reasons for the choice of the particular area is the fact of the other work going on in the Branch with this age group.

Mental Health Counseling in this context means dealing in a psychotherapeutic manner, through interviewing, with minor to moderately serious emotional disturbances. It does not mean the independent practice of psychotherapy. It is clearly understood by all participants in this project that these Counselors will work under supervision and will not be asked to diagnose their clients. Clients will be screened by experienced psychiatrists and the counseling itself will be done under careful supervision by NIMH personnel.

Methods Employed:

The experiment can be divided into four stages of unequal length: Recruitment, Selection, Training, and Evaluation. The first two have been completed. The third is in process; the fourth is in the planning phase.

In the Recruitment stage, we wanted to determine whether it would be feasible to locate a substantial number of women interested in taking this kind of training without any financial recompense even though they were told emphatically that it is an experiment with no guarantee of employment afterward. This was amply demonstrated, at least for the Washington area. As a result of about sixty telephone calls to individuals and organizations and six speeches, all of which occurred between mid-April and June 1, 1960, eighty women requested and received application blanks. No application blank was sent out without a ten-minute telephone conversation with the applicant explaining the project and emphasizing the risks. Forty-nine of the blanks were returned, filled out by people who could reasonably be considered as applicants.

The Selection stage took place between mid-May and June 28, 1960. Criteria for selection were as follows: (1) High general intelligence; (2) psychological perceptiveness about others and undefensive awareness about themselves; (3) integrity; and (4) sufficient emotional maturity to be able to work effectively together and to cope with the stresses of therapeutic work.

The Selection procedures included five steps in the following order. Some applicants either fell out or were dropped out at the end of each step so that only 14 arrived at the fifth step.

1. Application blank to be filled out.

2. An autobiography to be written by each applicant of about 1500 words in which she was asked to tell how she felt at the different stages of her development and how she thought she came to be the kind of person she is.

3. A group session which lasted from 9 A.M. to 3 P.M. The applicants were asked to come to the NIH for these sessions in groups of about 8. They were put through various tasks including interviewing and introducing each other, discussing a topic and arriving at a consensus, discussing a tape-recorded initial interview, and paper and pencil group tests. There were always at least two observers, usually three.

4. Individual tests and individual interviews. The tests were the Rorschach, a modified and abbreviated TAT, and three items of the Wechsler-Bellevue Scale. Each candidate had two $1\frac{1}{2}$-hour individual interviews, each one of the two with a different interviewer.

5. A final group session in small groups of about seven in each and a final individual interview, usually with a new interviewer.

On the basis of these procedures, eight trainees were chosen by a consensus of all those who had been engaged in the Selection procedures. Certain vital statistics which have been tabulated on all the applicants as compared with the selected candidates give a resonably clear picture of the similarities and differences. The median age is the same, namely between 40 and 44. The average number of children is approximately the same, namely between 2 and 3. The differences have to do

with education, psychoanalysis, husband's occupation, and own occupation. In each of these items the selected candidates on the whole had more or stood higher than the average applicant. In brief, all the candidates are college graduates. Two have, in addition, some work toward an advanced degree. Two have an M.S. One has a Ph.D. Four have had considerable psychoanalysis. One has had some psychotherapy. Their husbands' occupations all fall into the categories of major professions or executives. All but two of them have held paying jobs themselves at a professional level.

The Training Stage of the study has been in progress since September 12, 1960. The candidates have been asked to be prepared to schedule flexibly 20 hours a week of work outside their homes and in addition to do some reading which can be done at home. This permits the women to cover their domestic responsibilities and still to participate in an intensive, very practical, on-the-job course of training.

During the first few weeks the candidates were given an orientation and a series of lectures by various members of the NIMH staff from within and without the Branch. In the third week they began to settle in to a regular schedule. This includes at the present time the following nine items of which No. 8 is considered the most important.

1. A lecture course, two hours a week, on Personality Development, by Dr. Blanche Sweet.

2. A clinical seminar, two hours a week, by Dr. Charmian Elkes.

3. A clinical seminar, two hours every other week, by Dr. Margaret Rioch.

4. A seminar devoted to a discussion of reading material, two hours every other week, by Dr. Margaret Rioch.

5. A seminar on Family Dynamics, two hours a week, by Dr. Arden Flint.

6. A supervisory seminar in groups of four, two hours a week, by Drs. Elkes and Rioch.

7. Observation of live interviews by experienced therapists, about two hours a week.

8. Interviews by the candidates themselves with the normal control subjects at the various Institutes of NIH, about three hours a week. These are always tape-recorded and supervised by Drs. Elkes and Rioch. They are listened to and written up by the candidates themselves.

9. Placements in one of the following community agencies, four hours a week: D. C. Juvenile Court, Montgomery County Juvenile Court, U. S. Probation Service, Family Service Agency of Montgomery County, NIMH Study Center at Langley Park. In these agencies the candidates have observed interviews and in most of them they are now taking active part in the work of the agency by interviewing themselves under the supervision of experienced agency workers.

In addition to the overall hypothesis to be tested by this experiment, namely that carefully selected candidates can be trained in two years to perform Mental Health Counseling, the Training Stage is designed to investigate two particular questions. First, will a Training Program of this kind be successful in which the main teachers consciously and purposefully operate on the basis of removing pressures from the students insofar as they possibly can? There will be no examinations. There will be a minimum number of deadlines. There is a great deal of humor in the air. To use a shopworn phrase, the atmosphere is extremely permissive. This attitude presupposes a high degree of motivation on the part of the students which is indeed present.

Second, will a Training Program of this kind be successful which operates consciously and purposefully without any fixed system? This means that, whereas the students in their reading and course work become acquainted with various theories of personality and of therapy, they are nevertheless not taught any specific system under which they should operate in doing their own counseling. On the contrary they are encouraged to view all systems with a certain skepticism. This also means that their teachers make no attempt to present a uniform point of view either about theory of personality or practice in interviewing. The teachers have differing but on the whole rather broad electic points of view. Their general purpose is to help the students to become as aware as possible of what goes on in their clients and what goes on in themselves and on this basis to use themselves as positive therapeutic tools. The question to be answered is whether with this kind of teaching each student will find her own satisfactory style. The assumption to be investigated is that, given a mature, intelligently perceptive person who is not destructively oriented, her contact with a client will not be harmful and will be

increasingly helpful with training and experience. The further assumption is that it is unnecessary to define for the student in advance what her style will be, as distinguished from or as similar to techniques described in the literature as counseling, supportive or superficial or intensive psychotherapy.

Major Findings:

From the Recruitment Stage of the project, the conclusion is clear that this kind of program fills a real need felt by women around 40 for appropriate training in an occupation which is especially suited to their capacities. It is also clear that it is not difficult to find college graduates in this age group who are qualified for and eager to engage in this kind of training.

From the Selection Stage of the project no definitive statement can yet be made, but there is good evidence that the hypothesis to be tested by the Selection procedures is on the whole correct, namely that by the procedures outlined we could select trainees with aptitude for the training. This hypothesis, to be complete, should include the statement that the selectors are for the most part the teachers in the Training Program. This seems to ensure the selection of candidates with whom communication is easy for the teachers, who are themselves therapists, and who have apparently chosen a group of candidates whose values and ways of thinking are similar to their own. The limitation in this from the viewpoint of research into the process of selection is that there can be no answer to the question whether the applicants who were not selected might have turned out as well as or better than the ones selected. The system perpetuates the values and qualities of people who are at present successful therapists, but does not investigate the possibilities of using other values and qualities.

However that may be, there is general satisfaction among the teachers in this pilot project with the results of the Selection. Work is still in progress to determine to what extent the psychological tests should be considered a necessary part of the procedure. But the group sessions, followed by individual procedures for those not weeded out by the group sessions, were satisfactory methods for assessing the qualities of the applicants and can be recommended for the selection of trainees in programs having to do with interpersonal relations.

From the three months during which the Training Stage has so far been in existence a few observations have already been made which have relevance to the general field of training for therapy.

In general, the first things that had to be learned by the trainees were (1) how to be "professional" rather than social in an interview situation, (2) to pursue rather than evade areas of anxiety and discomfort which arose during interviews, (3) to recognize defensiveness and anxiety which arose in themselves as a result of what was discussed in the interviews, and thereby realizing the effect their own feelings had in impeding the progress of the interviews, (4) to listen to what the interviewee was saying and respond to that rather than to follow their own cues. Although this did not happen by design, it turned out that in this preliminary period more emphasis was placed on the manner of conducting an interview rather than on the content of the interview itself. The trainees had to progress from their first fumbling attempts which were characterized either by jerky questions and answers or over-reassurance or both, to situations where an interviewee could feel free to talk comfortably and intimately about himself. This has occurred with some of the trainees, who are becoming more able to look for and understand the underlying meaning of what is said to them.

The use of the normal control subjects as interviewees has been enormously useful in the early training period and the study of the trainees' recorded interviews is an invaluable teaching device. It produces very quick improvement in interviewing technique. It became clear, especially after first hearing a report of an interview and then the taped interview itself that the interviewer could not by and large report her mistakes. This was not because she wished to conceal them but because she did not know what they were. Otherwise she would not have made them. Listening to the interviews together with the trainees, the teachers are able to point out on the spot awkward, self-defeating maneuvers as well as excellent bits of therapeutic interplay. The trainee learns from her own self-observation in listening to the tapes as well as from what is shown to her by teacher and fellow students. Within one or two succeeding interviews the faults thus brought out into the open are markedly diminished. From an economic point of view, the investment in a tape recorder cuts down so drastically the number of supervisory hours needed for the achievement of smooth interviewing that it represents a major saving of time and money.

The group morale which has grown up in this project is an important factor in facilitating learning. The morale is so good that it is possible to point out her mistakes to a trainee in front of the group without pulling any punches and without her suffering any loss of face or of self-esteem. No one so far has indulged in any form of hostile,

competitive undermining of a fellow student, although all have been frank in their evaluations of each other's interviews. The homogeneity in age, social situation, educational background, and interests probably plays a role in this. The fact that this is a pilot study in which all are together in a new adventure is probably equally important.

Significance to Mental Health:

If the experiment in training Mental Health Counselors succeeds, it will demonstrate that truly low-cost psychotherapy can be provided by such Counselors for the mild to moderately serious disturbance if adequate supervision is available. This would be in line with the mental health services provided by the psychiatric technician in the U. S. Army Medical Corps and by the Family Discussion Bureau of the Tavistock Clinic in London.

Proposed Course of Project:

We propose to continue the training through June 1962. A preliminary evaluation of the results of the training will take place in the spring of 1961 and a final evaluation in the spring of 1962. The material gathered about the developmental process in moderately disturbed adolescents will be collated with that collected in the other two projects of the Branch which deal with the same age group.

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